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THE ACTION OF HYDERGINE IN NORMAL LABOUR*

BY

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THE theoretical basis for the use of antispasmodic drugs in labour is provided by Sauter's (1948a) views on uterine innervation and action. Expressed briefly, these are that uterine contractions are influenced rather than initiated by sympathetic and parasympathetic impulses, the former causing an increase in the tone of the uterus while parasympathetic stimuli have the opposite effect. It follows that a diminution in uterine tone could be produced either by parasympathicomimetic or sympathicolytic agents and that such a diminution in tone would result in an increase in the amplitude and hence in the efficiency of uterine contractions.

These views have recently been restated by Grasset and Gauthier (1953) and are to some extent in keeping with the findings of Caldeyro Barcia and Alvarez (1952).

Sauter concluded that the most suitable sympathetic relaxant for use in labour was Dihydroergotamine Methanesulphonate, originally synthesized by Stoll and Hoffman (1943) and reputed to lack the oxytocic and vasoconstrictor effects of Ergotamine while retaining its sympathicolytic action to an enhanced degree (Horton *et al.*, 1945; Orth and Ritchie, 1947; Rothlin, 1947).

Sauter himself (1948b) described a series of 43 cases of uterine inertia treated with Dihydroergotamine, a satisfactory response being observed in 30 patients—70 per cent. He concluded that the drug was of value in the management of long labour. Similar results were reported by Gill (1951) and Gill and Farrar (1951), while Baskin and Crealock (1950, 1951), investigating the effect of Dihydroergotamine on normal parturients, found that it caused a marked reduction in the duration of labour. Although the above observers were agreed that Dihydroergotamine exhibited no adverse effects upon either the mother or the foetus, Gill and Farrar (1951) noted in some of their cases an increase in the acme of the uterine contractions. This, however, was attributed to release from sympathetic over-activity rather than to any direct oxytocic effect of the drug upon the uterus.

Despite this view it was later apparent that Dihydroergotamine possessed a considerable oxytocic action to which, in some cases, foetal death could be attributed (Altman *et al.*, 1952). Probably for this reason its reception in Great Britain has, in general, been unenthusiastic and at the recent 13th British Congress of Obstetrics and Gynaecology both Jeffcoate (1952) and Moir (1952) condemned the drug as potentially dangerous.

HYDERGINE

This direct oxytocic action is apparently not shared by other hydrogenated alkaloids of ergot. A mixture of such compounds, available under the trade name of "Hydergine" and consisting of equal parts—0·1 milligramme per millilitre—of Dihydroergocornine, Dihydroergocristine and Dihydroergokryptine, is stated to provide the same spasmolytic action as Dihydroergotamine while lacking any side-effects attributable to direct uterine stimulation.

* The "Hydergine" used in this survey was kindly supplied by Sandoz Ltd.

The value of "Hydergine" in obstetrics was investigated by Wilhelm (1951), who concluded that the drug exerted a profound relaxant effect upon the cervix uteri during labour, while any oxytocic action was so weak as to be negligible. When given at a cervical dilatation of 3 centimetres the duration of labour was greatly reduced, full dilatation being reached within 1 to 2 hours. Furthermore, no adverse effect upon the condition of the infant at delivery or upon the behaviour of the uterus post-partum was demonstrated.

Present Investigation

The present paper is based upon an analysis of a series of potentially normal primiparae to whom "Hydergine" was given in the manner advocated by Wilhelm (1951). This series has been compared with a group of patients receiving no such treatment. It appeared likely that an investigation of this nature would be of value for the following reasons:

(1) It would reveal any adverse effects of "Hydergine" upon the foetus or the mother. These, although probably without serious import in normal labour, might constitute a contra-indication to the use of the drug in uterine inertia where the condition both of the foetus and, to a lesser extent, of the mother might already be impaired.

(2) It would enable any oxytocic action of "Hydergine" to be assessed. If this could be shown to be absent a reduction in the duration of labour following use of the drug could reasonably be attributed to its sympathicolytic effect.

(3) In attempting to determine the action of any compound it is essential that statistically acceptable comparisons be drawn between the treated cases and a control series. Such comparisons, although relatively straightforward in the case of normal primiparae, are less exact where prolonged labours are concerned, owing to the frequent occurrence of other complications apart from the inertia itself.

(4) Lastly, if it could be shown that "Hydergine", while possessing no undesirable side-effects, appreciably reduced the duration of labour, it would be reasonable to recommend its use in normal deliveries.

Selection of Cases

Since it was intended to confine the present investigation to potentially normal primiparae, cases showing one or more of the following conditions were excluded:

(1) Toxaemias of pregnancy and diseases coincidental with pregnancy.
(2) Presentations other than by the vertex.
(3) Multiple pregnancy.
(4) Ante-partum haemorrhage.
(5) Disproportion, proven or suspected.
(6) Labour occurring before 36 or after 42 weeks gestation.
(7) Known foetal abnormalities.
(8) Cases where the cervix was more than 3 centimetres dilated on arrival in the labour ward.

A primipara not falling into one or other of the above groups was assumed to be potentially normal and suitable for inclusion in the survey. On admission to the labour ward any such case was assigned a code number placing her in one of two categories, "A" or "B", the composition of which had been drawn up by means of a table of random numbers.

Method of Administration of "Hydergine"

"Hydergine" is available in ampoules containing one millilitre of the mixture of hydrogenated ergot alkaloids referred to above. These ampoules were matched by others containing a similar volume of sterile isotonic saline intended as a control injection. One set of ampoules was labelled "A" and the other "B", the precise identity of each set thus being kept from the labour ward staff. Each patient received the contents of one ampoule—given by intramuscular injection in 4 equally divided doses at half-hourly intervals—as soon as vaginal or, in some cases, rectal examination had shown the cervix to be between 2 and 4 centimetres dilated. Patients in Category "A" were given the contents of an "A" ampoule and those in Category "B" the contents of a "B" ampoule. Apart from these measures no special treatment was given to either category, management being solely in accordance with the obstetric requirements of the case.

Information was collected from both categories upon the following points:

I. *Labour*

(1) The duration of the first stage
  (*a*) From the start of labour to the first injection.
  (*b*) From the first injection to full dilatation.
(2) The duration of the second stage.
(3) The method of delivery of the infant and of the placenta.
(4) The amount of blood loss in the third stage.

II. *The Mother*

(1) Sedatives and analgesics given after the injections.
(2) Blood pressure and pulse rate before and after the injections.
(3) Subjective symptoms noted after the injections.

III. *The Infant*

(1) The foetal heart rate before and after the injections.
(2) The presence or absence of foetal distress.
(3) The duration of post-partum apnoea.

Results

In all, 95 cases were analyzed; of these 46 were given "Hydergine"—Category "A"—and 49 the control solution of sterile saline—Category "B". Comparison of the age groups of the mothers and of the weight distribution and sex ratio of the infants showed the two categories to be comparable.

The Duration of Labour

An analysis of the first and second stages of labour in Category "A" and Category "B" is shown in Table I. For statistical reasons comparison between the two groups of cases was made by using the logarithms of the times involved—in minutes. This method is of particular value in view of the fact that the mean of the logarithms is less affected by occasional outlying observations than the mean of the actual times themselves. In consequence the distribution of values is more symmetrical.

Study of Table I allows the following conclusions to be drawn:

(1) The similarity between the two groups for the period "Start of Labour to First Injection" provides further evidence that Category "A" and Category "B" are comparable, since this

Table I

		First Stage		
		Start of Labour to First Injection	First Injection to Full Dilatation	Second Stage
Category "A"	Mean $\log_{10}$	2·69196	2·33487	1·61109
	Standard Error (in $\log_{10}$)	0·3729	0·3989	0·2425
	Geometric Mean*	8 hrs. 12 mins.	3 hrs. 36 mins.	41 mins.
Category "B"	Mean $\log_{10}$	2·69486	2·32447	1·66326
	Standard Error (in $\log_{10}$)	0·4405	0·4409	0·2069
	Geometric Mean*	8 hrs. 15 mins.	3 hrs. 31 mins.	46 mins.
Comparison of Group Means	"t"	—	0·1203	1·0922
	D.F.	—	93	89
	P	—	0·55	0·14

D.F.: Degree of Freedom.
P.: Probability Value.
The "t" test reveals no significant difference between the mean logarithm of Categories "A" and "B" for any of the periods under consideration.

* The antilogarithm of the mean of the logarithmic values is known as the Geometric Mean as opposed to the more usual Arithmetic Mean.

period represents the time allowed to elapse before "Hydergine" was given.

(2) The lack of significance in the comparison between the two categories of the periods "Injection to Full Dilatation"—representing the remainder of the first stage—and "Second Stage" shows that there is no evidence that "Hydergine" has any effect upon the duration of either the first or the second stage of labour.

The Method of Delivery

As only potentially normal cases were included in the present investigation, the incidence of spontaneous delivery was high—93·7 per cent. In respect of the method of delivery little difference existed between the two groups under consideration. In Category "B"—the control series—there were 46 spontaneous and 3 forceps deliveries; the indications for the latter being foetal distress in 2 cases and delay in the second stage in the third. In Category "A"—"Hydergine" treated—there were 43 spontaneous deliveries, 1 forceps for foetal distress and 2 Caesarean sections for cervical dystocia after labours lasting 30 and 90 hours. These last 2 cases are of particular interest since it is in precisely such a type of dystocia that "Hydergine" is claimed to be of most value.

The Third Stage of Labour

No case of post-partum haemorrhage occurred in either category while the actual amounts of blood lost during the third stage were essentially equal in both groups. One manual removal of the placenta was necessary in a patient in Category "A", the indication being retention of the placenta for over 30 minutes. Judged by these results, "Hydergine" did not appear to influence the third stage of labour in any respect.

Other Possible Effects of "Hydergine" Upon the Mother

Although no significant difference existed between the two groups of patients, a slightly greater proportion of Category "B" cases required sedative or analgesic drugs during the first stage of labour. It is possible that in some cases "Hydergine" exerted a sedative effect, although no convincing clinical evidence for such a view was forthcoming.

"Hydergine" did not affect either the maternal blood pressure or pulse rate, such fluctuations as were observed being closely paralleled in the control group.

In 3 cases the strength and frequency of the uterine contractions appeared to increase after administration of "Hydergine". This may possibly have been due to a direct oxytocic action. In none of these cases did the condition of the foetus or of the mother give rise to concern.

The Effect of "Hydergine" Upon the Infant

As shown in Table II the incidence of foetal distress was apparently lower in Category "A" than in Category "B".

Although these figures are not statistically significant, they support the clinical impression that "Hydergine" exerted no adverse effect upon the foetus; an impression further born out by the observation that variations in the foetal heart rate and the duration of post-partum apnoea in Category "A" cases resembled in every way those noted in the control group.

Discussion

Two possible criticisms of the above analysis require answering. In the first place it may be argued that the present series is too small to allow of any definite conclusions to be drawn. Although it must be admitted that compara-

Table II

The Incidence of Foetal Distress

	No Foetal Distress	Foetal Distress as judged by: Heart Rate	Meconium	Birth Condition	Percentage Distressed
Category "A"	43	2	0	1	7
Category "B"	41	3	4	1	16

tively few cases have been analyzed, this investigation was intended to be more in the nature of a pilot survey than a full-scale review, its object being to demonstrate whether the effect of "Hydergine" was sufficient to be of real clinical value. Secondly, the stage of cervical dilatation at which the injections were given may appear to have lacked accurate confirmation and standardization. It must be borne in mind, however, that it was intended to determine whether a method simple enough to be widely and easily applicable could yield good results.

Having regard for the above considerations, it would seem that as far as can be judged from the present investigation, "Hydergine" has no effect upon the duration of labour and that even if analysis of a larger series of cases showed the drug to have some such effect this would almost certainly be too small to be of clinical value. Two observations offer further support to this conclusion. In the first place it would seem that the period extending from the onset of labour to a cervical dilatation of about 3 centimetres—an average (geometric mean) for all cases analyzed of 8 hours 14 minutes—is so much greater than the remainder of labour—3 hours and 34 minutes on the average—that only a great reduction in the latter period would appreciably alter the total duration. Secondly, as has already been mentioned, 2 cases of cervical dystocia were met with in Category "A", both of whom failed to respond to "Hydergine" and both of whom were ultimately delivered by Caesarean section. These cases are by no means isolated examples since in a further group of 24 cases of prolonged labour in which "Hydergine" was given no clear-cut effect upon the rate of cervical dilatation was observed.

On the other hand, as far as could be judged, "Hydergine" exerted no adverse side-effects upon either the infant or the mother, and indeed appeared to possess a certain sedative action in some cases. In addition, the direct oxytocic effect of the drug seemed to be inconstant and slight.

Summary

(1) A series of 95 potentially normal primiparae has been analyzed in order to determine whether "Hydergine", given by intramuscular injection, would effectively reduce the duration of labour.

(2) Of these cases, 46 were given the drug in question; the remaining 49 serving as controls.

(3) No statistically significant alteration in the duration of the first or second stages of labour was demonstrated.

(4) "Hydergine" did not appear to have any adverse effect upon the third stage of labour or upon the general condition of the mother or of the infant.

(5) The conclusion reached from this admittedly small group of cases is that "Hydergine" is unlikely to prove of value in the management of normal labour.

Acknowledgments

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THE EFFECTS OF ADRENALINE AND NORADRENALINE ON THE INTACT HUMAN UTERUS IN LATE PREGNANCY AND LABOUR

BY

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THE response of the intact human uterus to adrenal medullary hormones has for years been the subject of differing opinions. This confusion has often arisen from the scanty evidence put forward, the inadequate methods of investigation employed and, in retrospect, the crude nature of the preparations used.

Adrenaline B.P. (Epinephrine U.S.P.) when prepared from mammalian adrenal glands contains, according to the manufacturers, 15-20 per cent noradrenaline. As will be seen later the presence of this fraction may help to explain some, but not all, of the discrepancies of past work.

PREVIOUS OBSERVATIONS

In 1927 Rucker used adrenaline to relax pathological constriction rings. In the same year, Bourne and Burn (1927), making observations in two patients by means of a small hydrostatic intra-uterine balloon connected to a mercury manometer, found that adrenaline inhibited uterine contractions. In one patient they gave one massive dose of liq. adrenalinae B.P., 5 minims intravenously (i.e., 300 micrograms), and observed in their published tracing that one premature large contraction was followed by complete cessation of activity for 12 minutes, after which contractions recommenced.

Brown and Wilder (1943) used the same method, but only with one-tenth that dose of adrenaline, which is much nearer physiological levels. They obtained essentially the same tracings and interpreted these as showing an initial contraction followed by a compensatory pause, much like an extra-systole. Although other workers might read the tracings differently, they concluded that adrenaline "stimulates the human labouring and puerperal uterus to contraction".

Woodbury and Abreu (1944) then pointed out that the size of the dose is important, and obtained the same tracings as Bourne and Burn when 100 micrograms of adrenaline were given rapidly by intravenous injection. This they interpreted as stimulation, and went on to demonstrate that the same dose well diluted and given slowly over a period of several minutes inhibited contractions in established labour.

Using an external apparatus which records changes in the shape of the anterior abdominal wall consequent upon uterine contraction, Kaiser (1950) obtained records in labour when pure *l*-adrenaline and *l*-noradrenaline were given separately. He described inhibition with adrenaline and stimulation with noradrenaline.

PRESENT EXPERIMENTS

Method

Uterine contractions have been recorded by introducing a small hydrostatic balloon of about 8 ml. capacity into the uterus outside the membranes above the foetal head, following the methods used by Bourne and Burn (1927) and Moir (1944). This was connected to a mercury manometer or alternatively a water tambour, recording on a slowly revolving drum.

In the control period 5 per cent glucose solution in distilled water was set up as an intravenous drip infusion. A second such apparatus was then assembled with the addition of 4 micrograms per ml. of the drug in the 5 per cent glucose solution. At an appropriate time this was connected to the first drip apparatus and adjusted to deliver 4 to 10 micro-

grams per minute of the active drug for about 10 to 20 minutes.

The whole method was controlled by frequent blood-pressure and pulse-records at 2-minute, and later, 5-minute intervals. The foetal heart rate was observed frequently. To avoid undue concern for the patient the recording apparatus was kept out of sight. When sedation (viz., chloral hydrate, pethidine, nitrous oxide) was indicated by the stage of labour, it was given according to usual practice.

Results

l-Adrenaline. Fifteen doses of *l*-adrenaline hydrochloride were given intravenously to 10 patients in the later weeks of pregnancy or in labour. On all occasions the large coordinated uterine contractions were inhibited (Fig. 1). The amplitude was always diminished, the base line remained constant or was lowered, and the frequency of the contractions was usually decreased during the administration of the drug. If administered in labour, the relaxation between the inhibited contractions appeared on clinical observation to be incomplete, and the patient often complained of continuous dull backache.

Within 2 minutes of the withdrawal of the infusion a period of stimulation followed in all but 1 case. This period outlasted the initial period of inhibition and was recorded as increased frequency of contractions, variable changes in amplitude and, quite commonly, a rising base line.

In 2 cases the small rapid waves described by Alvarez and Caldeyro (1950) were observed in the period of relaxation between the large coordinated uterine contractions. With adrenaline these small waves increased in amplitude in one case and were unaffected in the other, while the larger coordinated uterine contractions showed the usual inhibition.

l-Noradrenaline. Fourteen doses of *l*-nor-

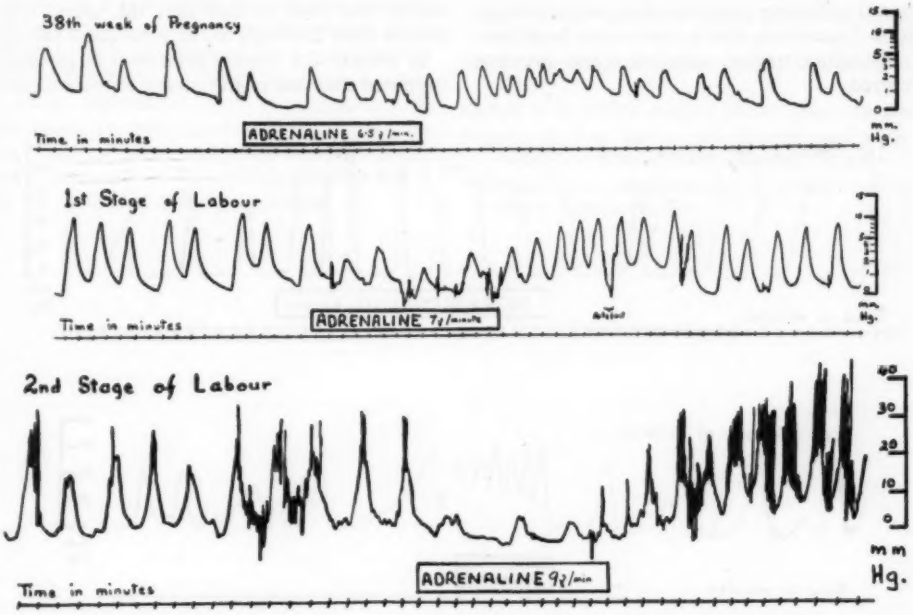

FIG. 1

Adrenaline by slow intravenous infusion causes inhibition of the large coordinated uterine contractions in late pregnancy and the first and second stages of labour.

adrenaline bitartrate have similarly been given to 10 patients in the later weeks of pregnancy or in labour. In each case the large coordinated uterine contractions were stimulated during the administration of the drug (Fig. 2). The contractions always increased in frequency and, with smaller doses, usually increased in amplitude. With larger doses the base line was commonly raised and the amplitude of the contractions was then decreased.

Weight for weight noradrenaline was found to be at least three times more active than adrenaline in producing the minimal response characteristic of each drug.

After withdrawal of the noradrenaline infusion a brief period of inhibition was observed in several cases. But this was in no way as obvious as the period of stimulation which so regularly followed the administration of adrenaline.

General Effects

At this dosage level (4-10 micrograms per minute) subjective symptoms were not produced, but on 2 occasions, after a momentary large dose of adrenaline, tremor, palpitation and sweating occurred.

Objective signs, however, were observed. *Adrenaline* caused marked pallor, tachycardia, deepened respiration and rising systolic blood pressure, but usually constant or falling diastolic pressure. In contra-distinction, with *noradrenaline* very slight pallor, bradycardia, deepened respiration and constantly elevated diastolic and systolic blood pressure were observed just as Barcroft and Konzett (1949) and others have found.

Discussion

It is interesting to find that so long ago as 1871 Sir James Y. Simpson believed "that though uterine contractions are no doubt guided or influenced by the brain or spinal cord, they are essentially independent of these organs". He based this opinion on the recorded cases of normal labour in human paraplegia, and on experiments done many years earlier. In these he removed the spinal cord in sows from the first dorsal vertebra downwards a few days before labour was due, to find that the uterus contracted quite normally in the subsequent labour.

In present-day clinical practice it is generally supposed that one of the causes of incoordinate

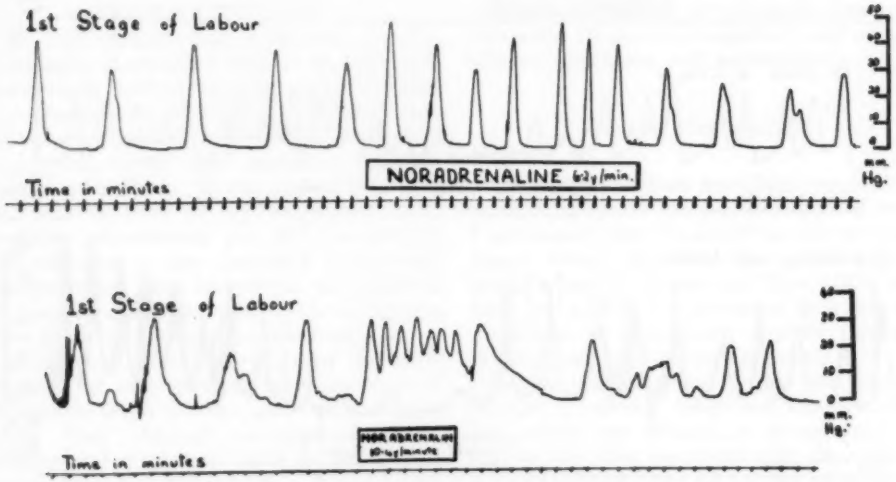

Fig. 2

Noradrenaline by slow intravenous infusion causes stimulation of the large uterine contractions in labour. With a greater dose, relaxation is incomplete between contractions.

uterine action in the human is some abnormality of the innervation of the uterus, that is, some abnormality of the function of the nerves which, to use Simpson's words, "guide or influence" uterine contractions.

Mann and West (1951) have examined efferent blood from the uterus in the cat by occluding the uterine veins, excluding the adrenals from the circulation by ligature, and then collecting specimens of the efferent blood from the ovarian veins. They found that, after stimulation of the hypogastric nerve, both adrenaline and noradrenaline appeared in the efferent blood in the concentration of 0·005 micrograms per ml. and 0·037 micrograms per ml. of plasma respectively.

It is very probable that the sympathetic nerves to the human uterus also produce both adrenaline and noradrenaline at their endings. Having regard now to the effects of adrenaline and noradrenaline demonstrated in the experiments described earlier in this paper, it is obvious that it would be necessary for the relative amounts of these substances liberated at the uterine nerve endings to be finely adjusted for normal coordinated contractions to occur. Similarly, it could be easily understood that maladjustment of these amounts could produce atypical contractions which, if continued, could well lead to the clinical condition of incoordinate uterine action with its customary protracted course.

Conclusions

(1) Adrenaline B.P. of animal origin is a mixture of adrenaline and noradrenaline.

(2) Pure *l*-adrenaline inhibits the large uterine contractions of late pregnancy and labour, whereas pure *l*-noradrenaline stimulates them.

(3) Incoordinate uterine action is possibly associated with a derangement of the normal fine adjustment of the amounts of adrenaline and noradrenaline liberated at the nerve endings in the uterus.

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AN EVALUATION OF MODERN TREATMENTS OF ECLAMPSIA

BY

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IN recent years there has been a fall in the number of maternal and foetal deaths from pre-eclampsia and eclampsia. Nevertheless, these conditions are still among the more serious complications of pregnancy, and the solution of their problems is yet to be discovered. The first line of attack concerns the pre-convulsant patient, and consists of the prevention, early diagnosis and treatment of pre-eclampsia. This article attempts to deal with the care of the convulsant patient, and it sets out what seems to be, in our experience, the best form of treatment for established eclampsia.

Material for the article has been collected from recent publications and other sources; altogether the various treatments employed in 1,718 cases of eclampsia have been analyzed and an endeavour has been made to determine the form of therapy most beneficial to the patient and her child.

RATIONALE OF TREATMENT

The treatment of any disease should follow the discovery of its cause, and be based on its correction or eradication. Unfortunately, this is not possible in the case of eclampsia, for it still remains the disease of unproven theories. Treatment, therefore, must be *ad hoc* and symptomatic in nature. Measures should first be directed towards controlling the fits, because it is their repetition which leads to the deterioration of the patient, and may end in her death. When they are controlled the pregnancy may be terminated (in ante-partum or intra-partum cases), as soon as it is consistent with the patient's safety. It behoves us, therefore, to study the mechanism whereby fits are produced, and then to describe the steps that may be taken to prevent their recurrence.

MECHANISM OF THE PRODUCTION OF FITS

In the eclamptic patient an external stimulus is often the immediate cause of the development of a fit. The fit occurs because the patient has been sensitized by one of the following four factors:

(1) A state of nervous hyperexcitability associated with the presence of cerebral oedema. This was suggested by Zangemeister in 1915 as part of his water-poisoning theory. Rowntree (1923) graphically demonstrated it in dogs, when he produced cerebral oedema, seen at post-mortem, by the injection of 50 ml. of water per kg. of body weight every half hour until fits occurred. Presumably, the excessive water retention in toxaemia leads to a similar mechanism in the eclamptic brain, so favouring the production of fits.

(2) An excessive retention of sodium ions. In toxaemia there is a retention of sodium ions in the body. These are mainly held in the extracellular spaces, but some increase in the intracellular sodium content also occurs. Among other cells the neurones of the central nervous system contain more sodium, as the mechanism for its removal, the "sodium pump", is deprived of energy by the enhanced suprarenal activity present in eclampsia (Carey). This results in increased neuronal excitability and encourages the production of fits.

(3) A state of hypertension. The occurrence of an eclamptic fit is usually preceded by a sudden rise in blood pressure, the convulsion being a manifestation of hypertensive encephalo-

pathy. Spasm of the central arterioles may lead to zones of cerebral anoxia, and initiate a convulsion.

(4) A predisposition to fits shown by cerebral dysrhythmia. Since the work of Lennox and others (1939), it has been shown that fits are prone to occur in patients who show an abnormal brain pattern on electroencephalography—cerebral dysrhythmia. This is seen in all epileptics during their seizures and in 90 per cent of them between seizures; it is also present in approximately 10 per cent of the general population. If pre-eclampsia occurs in a dysrhythmic individual, the likelihood of fits ensuing is much greater than when it occurs in a patient with a normal cerebral pattern. Thus Rosenbaum and Maltby (1943) found dysrhythmia was present in 65 per cent of 20 eclamptics, but in only 10 per cent of 20 non-convulsant pre-eclamptic patients.

Finally, when the overwhelming cerebral discharge has been produced by the hyperexcited cortex, it is conducted along efferent pathways to the skeletal muscles, where tonic and clonic contractions result, and the convulsion occurs.

Theoretical Modes of Treatment

There are a number of ways in which this eclamptogenic sequence may be interrupted, the most favourable being either in reducing the stimuli themselves, in diminishing their sensory perception, in aborting the motor discharge in the brain or in preventing the muscular paroxysm at the periphery.

(1) The avoidance of stimuli. This was first emphasized by Stroganoff and formed an integral part of the nursing technique of eclampsia, which he introduced in 1924. However, it is never very effective, as it is difficult to eradicate noise in a busy hospital, and some stimuli, such as uterine contractions during labour, cannot be avoided when dealing with an intra-partum case.

(2) The diminution of the patient's perception of stimuli. This again was advocated by Stroganoff, and it forms the basis of those sedative methods of treatment which are still greatly in vogue today. The most popular drugs employed for this purpose have been chloroform, chloral hydrate, paraldehyde, luminal, pethidine, pentothal and avertin. Heavy sedation, however, predisposes to pulmonary infection and, for this reason, the repeated administration of anaesthetics to eclamptic patients is inadvisable. The use of a potent liver poison such as chloroform is indefensible.

(3) The reduction of cerebral oedema. This has been attempted by the intravenous infusion of hypertonic saline and sucrose solutions or by the administration of hypertonic magnesium sulphate solution per rectum. Although these may be rapidly effective in reducing an increased intracranial pressure this is of no avail to the eclamptic patient, as an increased pressure does not usually occur in this disease; their effect in reducing oedema of the cerebral parenchyma present in eclampsia is much slower. Reduction of cerebral oedema, in fact, is too slow a process to benefit the eclamptic patient, who rapidly goes downhill when she has repeated fits.

(4) The increase of sodium ion excretion. This is an admirable form of treatment for the pre-eclamptic patient, but again it is too slow to arrest the succession of fits in the eclamptic subject.

(5) The reduction of hypertension. Drugs or techniques which are effective in reducing hypertension may be useful in eclampsia. Under their influence the blood pressure falls as the arterioles dilate, ischaemic cerebral foci are abolished and the convulsive process ceases. To be effective, however, the hypotensive agent should bring the blood pressure to below the level at which fits occur, it should be rapid in its action and prolonged in its effect. The drug should be free from obvious disadvantages in that it should be harmless to the mother and foetus, free from unpleasant side-effects and should not interfere with the progress of labour.

Hypotensive agents available are:

(*a*) Venesection. This is of limited value as the withdrawal of 12 to 20 ounces of blood produces only a temporary and limited fall of blood pressure. The procedure cannot be repeated with safety, and it predisposes to dangerous vasomotor collapse.

(*b*) Intravenous magnesium sulphate solutions. The fall in blood pressure is variable in its extent, whilst it is dangerous if more than 24 g. are

given in the 24 hours. Again there is a tendency to vasomotor collapse.

(*c*) Splanchnic block and caudal block. Paravertebral and intra-sacral injections of local anaesthetics, such as 1/2000 amethocaine hydrochloride, produce a marked and rapid fall of blood pressure which is wholly beneficial to the eclamptic patient. However, the effect of splanchnic block is only temporary and, as the technique is difficult and causes discomfort to the patient, it is not suitable for the frequent repetition necessary to maintain a prolonged fall of blood pressure. This disadvantage might be overcome by employing continuous caudal analgesia, but here again the operation may not prove easy or even possible, nor yet be free from other dangers.

(*d*) Hexamethonium salts. These have been used recently in a case of eclampsia by Penny and Shackleton (1951) with beneficial results. The compounds produce their hypotensive effect through a neurogenic mechanism exerted at the ganglionic level, while the hypertension of eclampsia is known, since the work of Kellar and Sutherland (1941), to be humoral in its origin. Morris (1953) has shown that their use in the pregnant patient is attended by dangers to the foetus (post-partum paralytic ileus and bronchopneumonia). They are unlikely, therefore, to meet with general approval.

(*e*) Veratrum viride. This extract of the green hellebore plant was introduced into medicine as a treatment for eclampsia by Barker in 1857. Its use was attended by many unpleasant side effects, and so its popularity waned and the drug was generally discredited. However, in 1940 a purified extract, marketed under the name of Veratrone, was re-introduced by Bryant and Fleming (1940) for the treatment of eclampsia, in closely controlled dosage. Veratrone is a 0·25 per cent aqueous solution of the alkaloids of veratrum viride, and its use is practically free from toxic side effects. The drug fulfils the requirements outlined above, being rapid in its action when given by intramuscular injection, suitable for repeated administration and harmless to mother and foetus. If the treatment of eclampsia by hypotensive methods can be shown to be of value, it is evident that this drug might prove to be useful.

(6) The abolition of cerebral dysrhythmia. Although temporary alterations in the electroencephalographic pattern may be obtained by the use of appropriate sedative and other drugs, they do not necessarily change the essential predisposition of the patient to convulsions. Furthermore, this type of therapy would be useless in those eclamptic patients who have a normal rhythm in their cerebral picturegrams.

(7) The paralysis of motor nerves and skeletal muscles. This mode of treatment has been utilized by Bennett (1941), who employed curare in a case of status epilepticus, but the result was not encouraging.

To summarize, therefore, the best methods of controlling eclamptic convulsions appear to be by the avoidance of stimuli, by the diminution of their perception through the use of sedative drugs, by the reduction of the raised blood pressure through the employment of hypotensive agents, or by a combination of all three methods. With a view to determining which form of therapy yields the best results for mother and child, the different treatments given by various authorities to 1,718 cases of eclampsia have been classified into three groups—treatment by sedation alone, treatment by sedation and hypotension combined and treatment solely by hypotension—and the mortality rates appropriate to each have been calculated.

I. Treatment by Sedation

The principal authorities employing sedation as a method of treatment, and the results they achieve, are set out in Table I.

These authorities favour a variety of sedative drugs, but essentially all employ a modification of Stroganoff's technique. (Cases in which avertin has been used are omitted from Table I, for reasons which will be discussed below.) A brief summary of their methods is given.

Authority A

During the first 9 years sedation was obtained by morphia and chloral hydrate; for the last 7 years morphia and nembutal have been used, together with 300 ml. of 30 per cent glucose solution intravenously and 10 ml. of 10 per cent calcium gluconate given 8-hourly. During the

TABLE I

Authority	Years	No. of cases of eclampsia	Maternal deaths	Foetal and neonatal deaths
A	1935–1943 and 1946–1952	83	5	36
B ..	1938–1950	211	17	Not stated
C ..	1939–1952	597	49	160
D ..	1945–1949	44	2	13
E ..	1947–1952	56	2	8/36
F ..	1948–1950	27	0	7
G ..	1950–1951	34	2	9
H ..	1950–1952	19	4	12
Total ..		1,071	81	245/840

first period 45 mothers were treated with 2 deaths (mortality rate of 4·44 per cent) and 19 foetuses died (mortality rate of 42·22 per cent). During the second period 3 of 38 mothers died (7·89 per cent) with the loss of 17 foetuses (44·74 per cent). The overall maternal mortality is 6·02 per cent, with a foetal loss of 43·37 per cent.

Authority B

From 1938 to 1950 in one hospital 162 cases of eclampsia were treated with morphia and subcutaneous magnesium sulphate solution, combined with chloroform inhalations for examinations and injections. Eleven maternal deaths resulted (6·79 per cent).

From 1947 to 1949 in another hospital 49 cases were treated with intravenous morphia, intramuscular or rectal paraldehyde, intravenous magnesium sulphate and 10 per cent or 20 per cent glucose solutions. There were 6 maternal deaths (12·25 per cent).

The total number of cases treated, therefore, amounts to 211 with 17 deaths (8·05 per cent). The foetal mortality rate is not given.

Authority C

From 1939 to 1944, 261 eclamptics were treated by oral chloral hydrate and potassium bromide, rectal paraldehyde and subcutaneous morphia and sodium phenobarbitone. Coincident with this, bowel wash-outs and purgatives were administered and occasional gastric lavage. There were 29 maternal deaths (11·11 per cent) and 100 foetal deaths (38·32 per cent).

From 1945 to 1950 treatment by magnesium sulphate was introduced, and of 260 eclamptic patients 13 mothers died (5·00 per cent) and 51 foetuses were lost (19·61 per cent).

In 1951 and 1952, 76 eclamptics were treated by morphia and intramuscular paraldehyde or sodium gardenal. Ten ml. of a 50 per cent solution of magnesium sulphate were given intramuscularly, and repeated in 2 ml. doses at 4-hourly intervals or when fits recurred. Caudal anaesthesia was also used for delivery and to control the blood pressure. A hexamethonium compound was used on 1 occasion. With this routine 7 mothers have died (9·21 per cent) and 9 foetuses have been lost (11·84 per cent).

The overall figures, therefore, for 597 eclamptics treated by varying methods, but in all of which sedation has been the chief therapeutic weapon, are 49 maternal deaths (8·21 per cent) and 160 foetal deaths (26·80 per cent).

Authority D

Forty-four cases of eclampsia were treated by morphia and intravenous magnesium sulphate. On some occasions 50 per cent glucose was given intravenously, and the sedation was reinforced by luminal and pentothal. Two mothers died (4·54 per cent) and 13 foetuses were lost (29·54 per cent).

Authority E

In this group there are grouped together the results of 8 workers, each of whom treated too few patients individually to obtain significant results.

From 1947 to 1952, 56 cases were treated by

different forms of sedation, comprising morphia, phenobarbitone, paraldehyde (rectally and intramuscularly), magnesium sulphate subcutaneously, pethidine, chloral hydrate, nembutal and pentothal, whilst some were given, in addition, intravenous glucose and calcium gluconate. Altogether there were 2 maternal deaths in this series (3·57 per cent), and from the workers who quote the appropriate figures 8 foetuses were lost from a total of 36 (22·22 per cent).

Authority F

Twenty-seven eclamptic patients were treated between 1948 and 1950 without the loss of a mother, and only 7 foetuses (25·92 per cent). The treatment of these patients consisted of morphia, combined with 15 per cent magnesium sulphate given intramuscularly.

Authority G

During 1950 and 1951, 34 eclamptic patients were treated with morphia, chloral hydrate and 5 to 10 ml. of 50 per cent magnesium sulphate solution given intravenously. In some cases 6 drachms of paraldehyde in olive oil were also given per rectum, whilst others received sodium gardenal, phenobarbitone, and pethidine. Two mothers died (5·88 per cent) and 9 foetuses were lost (26·47 per cent).

Authority H

From 1950 to 1952, 19 patients were treated mainly by sedation consisting of morphia and paraldehyde. Two mothers were lost and 2 died before receiving treatment (21·05 per cent), whilst 12 foetuses died, including 4 foetuses from the fatal cases who all died undelivered (63·16 per cent).

These figures provide a fair estimation of the value of the sedative treatment of eclampsia (excluding avertin) during recent years. In all cases the treatment has been in leading hospitals, carried out under the supervision of experts, with full adjuvant treatments available for shock, haemorrhage, induction of labour and the actual delivery. It will be seen, accordingly, that, of 1,071 cases of eclampsia occurring between 1935 and 1952, 81 mothers died. This corresponds to an overall maternal mortality rate of 7·56 per cent, the rates of individual workers varying between nil and 21·05 per cent. From the figures available, that is, from 840 patients, 245 stillbirths and neonatal deaths occurred, corresponding to a foetal mortality rate of 29·17 per cent, individual rates varying between 25·92 and 63·16 per cent.

If the cases occurring in the last 5 years are analyzed, it will be found that during this time, with all modern therapeutic advances available, 6 patients out of 80 died (7·50 per cent) with the loss of 28 foetuses (35·00 per cent). The result to be expected from sedative treatment, therefore, is the loss of 7·5 per cent of the mothers and about 30 per cent of the infants.

II. Treatment by Bromethol

Because of the recent popularization of bromethol (or avertin) as a method of treatment for eclampsia, the results obtained from its use have been classified separately. Although first used by Conrad (1927) for the treatment of eclampsia, it is only since Dewar and Morris (1947) reported a series of 45 cases treated by this method that interest in it has grown. The technique employed is fully described by these authors, but, briefly stated, the routine is to employ 0·0875 ml. of bromethol per Kg. of body weight, made up into a 3 per cent solution in distilled water at 40° C, and administered rectally after a preliminary Congo Red test to exclude the presence of dibromvinyl alcohol and tribromacetaldehyde HBr which cause sloughing of the rectum. The dose may be repeated at 3-hourly intervals up to a maximum of 6 doses in 30 hours. Whilst under its influence the patient's fluid balance is maintained, and calcium gluconate and hypertonic dextrose solutions are given intravenously (Campbell and Burton, 1952). Labour is induced after the first dose of bromethol if the cervix is patulous; if the os is closed and the case is one of mild degree, the patient is treated conservatively and labour is induced 24 to 48 hours after the eclamptic crisis has passed, but, if the eclampsia is severe in type, delivery by Caesarean section is preferred.

Some results of bromethol treatment are shown in Table II.

TABLE II

Authority	Date	Number of cases	Maternal deaths	Foetal and neonatal deaths
Dewar and Morris ..	1947	45	3	17
Campbell and Burton ..	1947–1951	36	0	10
Authority J	1947–1952	60	2	Not stated
Authority H	1950–1953	8	1	2
Total		149	6	29/89

Dewar and Morris, in their article, include only 2 maternal deaths in their series. However, as one patient died before the treatment could be administered, this third death should be included, for delay due to the lengthy preparation and administration of the drug is an inherent defect of this treatment, and should be allowed for in assessing its value. Furthermore, other workers whose figures are quoted in this analysis have included similar deaths occurring in their series of cases.

Of these 149 cases 6 patients died, giving a maternal mortality rate of 4·03 per cent, approximately half that associated with other methods of sedation. The foetal and neonatal deaths amount to 29 out of 89 cases (excluding any neonatal mortality among Campbell and Burton's cases, which is not stated), yielding a combined mortality rate of 32·58 per cent. Bromethol, therefore, from the mother's point of view, may be considered the most promising sedative for use in eclampsia, although it shows no increased efficacy in saving foetal lives. Its enhanced value to the mother is probably due to the fact that, in addition to its sedative properties, it is a hypotensive agent, and following its administration the blood pressure drops by an average of 50 mm.Hg. After its administration, therefore, the resultant sedation, combined with the lowered blood pressure, renders the occurrence of further fits unlikely. Thus only 3 of Dewar and Morris's patients had a further fit after treatment was begun. Five of Authority J's patients had 1 further fit and 2 had 2 additional fits. Campbell and Burton found that the fits continued in one-quarter of their patients, but this they ascribe to their lack of familiarity with the method. Treatment with bromethol, therefore, is a method which combines the two basic approaches to the problem of eclampsia, namely, the establishment of sedation in association with the lowering of the blood pressure.

Bromethol is of value in treating patients in their own homes and rendering them fit for transport to hospital. This involves the preparation of a standard dose (usually for a patient weighing 12 stone), which is maintained at body temperature in a thermos flask and taken to the patient. It has, however, some disadvantages in addition to its difficult preparation. Thus part of the dose may be returned following its instillation into the rectum, and this procedure itself is difficult to accomplish during the second stage of labour. Furthermore, it necessitates weighing the patient, which is not very practicable for the eclamptic subject; it should not be given to a comatose patient who has râles in the lungs and an absent cough reflex; experiments with dogs have shown it to be a liver and kidney poison, although this has not been demonstrated clinically.

III. Treatment by Veratrone

In comparison with these results figures are now presented to illustrate the value of purely hypotensive treatment. Here no attempt is made to reduce stimuli or to effect sedation, but the fits are abolished by reducing the blood pressure and eliminating the hypertensive encephalopathic process. Several series of eclamptic patients treated by Veratrone have been published to date, the largest being that of Garber and his colleagues (1950). These workers have treated 196 cases with only 3 maternal deaths, 2 of which were due to sepsis and occurred some time after the toxaemia had subsided. Bryant (1948) treated 168 patients and also had

3 maternal deaths, 2 resulting from sepsis, 1 of which occurred 14 days and the other 65 days post-partum.

The next largest series is our own comprising 80 cases of which 2 patients died, both from cerebral haemorrhage which occurred before admission to hospital. The results of treating 498 patients by Veratrone are shown in Table III.

It will be seen that 9 mothers died out of a total of 498 cases, giving a maternal mortality rate of 1·81 per cent, the West Middlesex Hospital mortality rate being 2·50 per cent. The foetal and neonatal deaths are not always quoted by these authors, but we have collected details of 123 infants, of whom 35 were lost—a mortality rate of 28·46 per cent. At the West Middlesex Hospital 22 infants were lost, an incidence of 27·50 per cent. For purposes of direct comparison the mortality rates resulting from the different methods of treatment are shown in Table IV.

Although the maternal mortality rates differ according to the technique of treatment employed, being biased in favour of hypotensive treatment, their statistical significance has not been determined, as it is felt that so many variables are involved that the figures are not amenable to this analysis. It is evident, however, that it will be of value to direct some attention to the technique of Veratrone treatment, for the low maternal mortality rate (1·81 per cent) obtained from some 500 cases is in marked contrast to the mortality rate (7·56 per cent) resulting from the more popular sedative treatments used in over 1,000 cases.

Pharmacology of Veratrone

Veratrone is an aqueous solution containing 2·5 mg. per millilitre of the ether-soluble alkaloids of veratrum viride. This is obtained from the roots and rhizomes of the green hellebore, a plant which grows in Canada and the north-eastern states of the U.S.A. It is standardized by the bio-assay of its vaso-depressor effect in dogs, this being an accurate method yielding a solution of constant and known potency. The principal alkaloids it contains are germitrine, neogermitrine, germidine, veratridine, protoveratridine and jervine.

An understanding of the pharmacological

Table III

Authority	Date	Number of cases	Maternal deaths	Foetal and neonatal deaths
Bryant	1948	168	3	Not stated
Garber *et al.*	1950	196	3	11/40 (reported in 1947)
Assali	1950	22	0	Not stated
Rhoads and Schmidt ..	1951	25	1	Not stated
Baird and Assali ..	1951	3	0	Not stated
Alban *et al.*	1952	4	0	2/3
West Middlesex Hospital	1940–1953	80	2	22
Total		498	9	35/123

Table IV

Mode of treatment	Number of cases	Maternal mortality rate Per cent	Number of cases	Foetal and neonatal mortality rates combined Per cent
Sedation	1,071	7·56	840	29·17
Sedation and hypotensive (bromethol)	149	4·03	89	32·58
Hypotensive (Veratrone) ..	498	1·81	123	28·46

actions of the individual alkaloids is a problem of some complexity and has as yet been incompletely elucidated; enough is known, however, from research work carried out mainly on dogs to provide a working knowledge of the way these substances exert their effects.

Intramuscular and intravenous injections of Veratrone in man produce a fall in blood pressure which is maximal in 10 to 15 minutes, and which persists for 1 to 2 hours. This is accompanied by a slowing of the pulse rate which also is temporary. Animal experiments show that there is at the same time a transient fall in hepatic-portal and renal blood flow, although a normal urinary output occurs, in man, if the blood pressure is maintained within the range 120-140/80-90 mm.Hg. The cardiac output is not decreased.

When Veratrone is given to conscious patients they may notice a feeling of generalized warmth and flushing. Only in marked overdosage are unpleasant side-effects produced; these comprise nausea, vomiting and a sub-sternal choking sensation.

Experiments in dogs have shown that the hypotension is produced by a blockade of the carotid sinus pressor reflex. This reflex mechanism maintains the height of the blood pressure, and when it is paralyzed by veratrum alkaloids marked hypotension ensues. The site of the blockade is probably placed centrally in the medulla, so that the fall is due to vaso-dilatation resulting from inhibition of the tone of the vaso-motor centre itself. This explains the experimental findings that atropinization and section of the vagi, in animals, have no effect upon the extent of the blood pressure fall. The isolated perfusion of Veratrone into the dog's head alone produces generalized hypotension, whilst perfusion of the isolated body has no such effect.

The bradycardia, however, is produced by a different mechanism. The veratrum alkaloids here stimulate the afferent branches of the vagus in the heart, which reflexly stimulate efferent cardio-inhibitory vagal para-sympathetic fibres, thereby producing the slowing of the pulse. This effect is neutralized by atropinization and by section of the vagi, whilst isolated perfusion of the head has no effect upon the heart rate. Perfusion of the isolated body, conversely, produces marked bradycardia resulting from the stimulation of the afferent vagal fibres, whilst no profound hypotension is produced, the blood pressure being regulated by the vaso-motor centre.

A small component of the fall in blood pressure may result secondarily from the bradycardia, but the dramatic early and sudden fall is essentially due to a distinct action on the carotid sinus pressor reflex. This hypotension may be abolished by the administration of adrenalin which acts directly on the peripheral arterioles, whilst the bradycardia, as explained above, may be reversed by giving atropine, which relieves the enhanced parasympathetic tone in the heart.

Veratrone has a wide range of safety, and an adequate therapeutic response is obtained without the production of toxic side-effects. Tolerance to the drug only develops after days or weeks, and within that time response to the drug does not become diminished with repeated doses; when treating eclampsia the opposite effect is frequently observed and the same degree of lowering of the blood pressure may be produced by smaller doses than before. In practice there is consequently no difficulty in maintaining the blood pressure at a normal level and well below that at which fits occur.

Technique for the Use of Veratrone

The Veratrone treatment of patients suffering from eclampsia is as follows:

(1) On admission to hospital the patient is isolated, and attended by special nurses. This isolation is not considered an important factor in the treatment of eclampsia, but the nursing of such patients in a general ward can only have an adverse psychological effect on the other mothers. A darkened room is unnecessary, and no special quietness is demanded.

(2) Ten minims (0·6 ml.) of Veratrone are given intramuscularly immediately. Unless the blood pressure rises further Veratrone is not given for 30 minutes, as some patients show a delayed response to the first dose. After this, blood pressure and pulse are recorded every 15 minutes, and Veratrone is repeated until the systolic pressure is below 120 mm.Hg. or the

pulse rate is down to 60 a minute. Thereafter, until the patient is conscious, no more Veratrone is given unless the blood pressure rises over 150 mm.Hg systolic pressure, provided that the pulse rate is not slower than 60 per minute. A typical chart showing the response to Veratrone is shown in Fig. 1. When the patient is conscious and co-operative 3 to 5 minim doses of Veratrone are given if she has nausea, severe headache, marked visual disturbances, epigastric pain or convulsions (with precautions as to blood pressure and pulse as above).

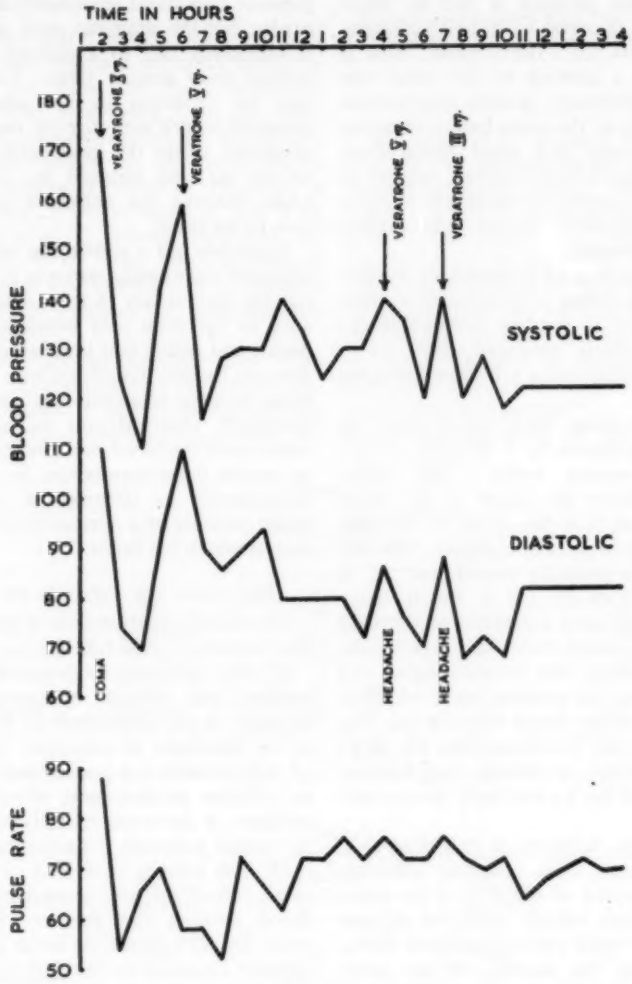

FIG. 1

Chart showing the response of the blood pressure and the pulse rate to Veratrone treatment in a case of eclampsia.

(3) Ten ml. of 50 per cent magnesium sulphate are given by intramuscular injection on admission, then 5 ml. every 6 hours for 4 days, and then 5 ml. every 12 hours for a further 4 days. If these injections are given deeply into the muscle abscess formation is less likely to follow than when they are given more superficially.

(4) The patient is catheterized as often as is necessary. If she is in labour and the rectum is loaded she should be given an enema.

(5) Pulse rate and blood pressure are recorded every quarter of an hour and the foetal heart rate is recorded hourly.

(6) No sedatives are given except for extreme restlessness or labour. During coma the patient should be turned from one side to the other at 2-hourly intervals.

(7) Fluid intake and urinary output are measured and charted. Urine is tested daily for albumen.

(8) A low salt diet is instituted as soon as possible.

When the eclampsia occurs during pregnancy the latter is treated conservatively until the fits are controlled, and the patient's condition has improved sufficiently to stand labour. Surgical induction of labour is then performed, usually by digital separation and simple rupture of the membranes. Delivery is allowed to take place spontaneously. Forceps are only applied for the usual obstetrical indications. In cases of disproportion, or when labour fails to follow induction, delivery may be effected by Caesarean section provided the patient's general condition is satisfactory and she has had no fits for 24 hours.

Anaesthesia

Nitrous oxide is to be preferred when anaesthesia is necessary. Chloroform, trilene and other toxic substances should be avoided.

Analysis of West Middlesex Hospital Series

Eighty eclamptic patients were treated during the years 1940 to 1953, according to the Veratrone technique described above. They comprise a representative series of obstetric patients, 25 being below 26 years of age, 46 being between 26 and 35 years and only 9 exceeding 36 years of age. The primiparae numbered 62 (77·5 per cent) and the multiparae 18 (22·5 per cent). No case of twin pregnancy was treated in this series.

Eclampsia occurred earlier than the 28th week of pregnancy in only 1 patient (1·2 per cent), between the 28th and 35th weeks in 19 patients (23·8 per cent), and later than this in 60 patients (75·0 per cent). Ante-partum eclampsia occurred on 45 occasions (56·3 per cent) and was often met with in an unbooked patient who was sent to hospital as an emergency case, sometimes in coma, having had one or more fits before admission. In 17 cases (21·3 per cent) the eclampsia was intra-partum in type, and 18 patients (22·4 per cent) suffered from post-partum eclampsia.

In the series 2 patients died (mortality rate 2·5 per cent), both patients having ante-partum eclampsia and being admitted in coma. In each case massive cerebral haemorrhage had occurred, the cerebrospinal fluid resembling pure blood when withdrawn by lumbar puncture. In both patients the diagnosis was confirmed by post-mortem examination, which showed extensive disintegration of the brain structure by profuse intracranial haemorrhage.

Fifteen stillbirths occurred in this series, 1 abortion and 6 neonatal deaths, giving a combined foetal-neonatal mortality rate of 27·5 per cent.

Discussion

Although today the incidence of eclampsia has diminished the disease is still of sufficient importance to merit the examination of new methods of treatment. It is our belief that the Stroganoff treatment and its modifications, with its 7·5 per cent maternal mortality rate is unsatisfactory, when more efficacious forms of therapy are available. Bromethol is associated with a maternal mortality rate of about 4 per cent, and for those wishing to employ sedatives this is the obvious one to use. Possibly, with more experience of this drug, the mortality rate may be lowered still further. The increased efficacy of bromethol is due to its hypotensive action, which is not shared by any other of the sedatives quoted in this analysis (with the possible exception of magnesium sulphate solutions). It seems only logical, therefore, if hypotension confers this supremacy on bromethol,

to expect that a more effective form of hypotensive therapy would yield still better results. This we hope to have shown in our analysis of the Veratrone series of cases, in which the maternal mortality rate is only 1·81 per cent. Of a thousand patients treated by sedation 75 may be expected to die, whereas of a thousand patients treated with Veratrone only 18 may die. Although critics of Veratrone treatment affirm that alternative methods are equally effective, no clinician has been able to match the figures of Garber and his associates, who in treating 196 patients with Veratrone had only 3 fatalities, 2 of these being due to sepsis.

Veratrone, we must admit, yields no improvement in the foetal and neonatal mortality rates. Here is a problem still awaiting solution. The technique of Veratrone administration requires good nursing with frequent and accurate recordings of the blood pressure and pulse rate. The rapidity of the fall of blood pressure does not appear to harm the eclamptic patient in any way but, on the contrary, is wholly salutary.

In conclusion it seems that hypotensive treatment, as exemplified by Veratrone, produces the best results for the eclamptic mother, and its use is unattended by any great disadvantages.

Summary

(1) The factors governing the occurrence of the eclamptic seizure are described, and the theoretical ways in which the process can be aborted are discussed.

(2) Different techniques for reducing the hypertension in these patients are examined, and the superiority of the purified extract of veratrum viride (Veratrone) is described.

(3) The results of treating 1,718 cases of eclampsia by sedation and hypotensive agents are contrasted and compared.

(4) The pharmacology of Veratrone is outlined, and its employment in the treatment of an eclamptic patient is described.

(5) An analysis is presented of 80 eclamptic patients treated with Veratrone at the West Middlesex Hospital.

(6) The maternal mortality rate is shown to be at its lowest with Veratrone treatment (1·81 per cent), whilst the foetal and neonatal loss remains approximately the same as when other methods are used.

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THE IMMEDIATE PROGNOSIS IN TOXAEMIA OF LATE PREGNANCY

BY

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THE "diagnostic ashcan of obstetrics" and a "cloak for ignorance" are terms which Jones (1941) has used to describe "toxaemia of late pregnancy". However, the title has the merit of being comprehensive in its scope and, reduced simply to toxaemia, it has commendable brevity. This paper deals with the results in a consecutive series of toxaemia, the patients being delivered in the Royal Maternity Hospital, Belfast, between the years 1946 and 1950.

THE MATERIAL

Patients were classified as suffering from toxaemia if they developed hypertension and/or proteinuria and if these signs were confirmed after admission to hospital. Cases were included in the series if the systolic blood pressure exceeded 150 and/or the diastolic blood pressure exceeded 90. A blood pressure of 140/90 merited inclusion if oedema was present as an additional sign. A trace of albumen in a catheter specimen of urine meant the inclusion of the patient, providing that urinary infection was not the causative factor. Transient hypertension and proteinuria are common findings in labour and, if such cases are included, a false impression of the incidence and the results is given; patients having hypertension or proteinuria in labour were excluded from the series unless these signs were known to be present before the onset of labour.

During the years under review 8,494 patients were delivered in the hospital. Toxaemia, as previously defined, was found in 1,420 cases, i.e., 16·7 per cent, of which 57 per cent had attended the hospital antenatal clinic on at least 2 occasions and might therefore be termed booked cases.

Dawson (1942), in New Zealand, found that 4·33 per cent of his patients developed toxaemia. Jones (1941), Hamilton *et al.* (1949) and Nordenstrahl (1951) each report an incidence of 5·8 per cent. The nearest approaches to the incidence in this series are those of Dubrauszky (1948), 14·8 per cent, and of Vara and Vehniainen (1951), 14·67 per cent. It may be argued that the high incidence of toxaemia in this series is due to the inclusion of many mild cases, but if the cases are graded by severity into 3 groups, as shown in Table I, it will be seen that only about one-third were mild. For the purpose of grading, mild cases had a blood pressure which did not exceed 150/100 and/or one-plus proteinuria. In moderate cases the upper limits were raised to 170/105 and two-plus proteinuria; patients with excessive hypertension, uncomplicated by proteinuria, were graded in this group. If the hypertension exceeded 170/105 and/or the urine contained three-plus proteinuria the case was graded as severe; all cases of eclampsia were included in this group.

TABLE I

Severity of Toxaemia

	Mild Group	Moderate Group	Severe Group
No. of Cases	456	645	319
Percentage	32·1	45·4	22·5

CLASSIFICATION OF CASES

"Toxaemia of late pregnancy" is a collective term which includes four separate disease entities, pre-eclamptic toxaemia, eclampsia, chronic hypertension and chronic nephritis. Browne (1946a) has discussed the differential diagnosis of these diseases and his criteria have been rigidly applied in the preparation of Table II.

It will be seen from Table II that 53·7 per cent (763 cases) remain unclassified. This figure is disappointingly high and shows a failure to distinguish between chronic hypertension and pre-eclamptic toxaemia. Two reasons for this failure may be mentioned. Firstly, chronic hypertension may be established as the diagnosis if there is a dependable history of this condition before the pregnancy commences. Examination of hospital records in retrospect is not the best method of obtaining this history and, because of this disadvantage, cases of chronic hypertension were undoubtedly missed and must remain unclassified. Secondly, one of the criteria which was employed in establishing a diagnosis of pre-eclamptic toxaemia was the recording of a normal blood pressure before the 20th week of pregnancy; Dieckmann (1952b) and Eastman (1950a) use the 24th week, but use of their criterion did not reduce the number of unclassified cases. As many of the patients failed to attend the antenatal clinic early in pregnancy, and as many were emergency admissions with established toxaemia, opportunity for using either criterion in diagnosing pre-eclamptic toxaemia was not available and such cases must also remain unclassified. Indeed, it is doubtful if the absence of hypertension before the 20th or 24th week of pregnancy should necessarily exclude a diagnosis of chronic hypertension. Patients with chronic hypertension often show a temporary fall of blood pressure during the middle trimester of pregnancy and it is possible that some of the cases classified as pre-eclamptic toxaemia have been, in fact, cases of chronic hypertension.

For comparison, the classification in certain reported series has been included in Table II. With the exception of Tillmann (1951), the incidence of pre-eclamptic toxaemia is much greater in these series and no cases have defied classification. One is bound to conclude that the disadvantages, which have been mentioned above, were not encountered or that different criteria were used for classification.

Maternal Mortality

Maternal mortality varies widely in published reports and depends largely on the severity of the toxaemia. In eclampsia the mortality varies from 16·1 per cent (Bernstine and Prince, 1947) and 15·2 per cent (Ross, 1947) to 1·5 per cent (Garber *et al.*, 1950). If all cases of toxaemia are included, the figure varies from 2·8 per cent (Wellen, 1940) to 0·3 per cent (McLane and Kuder, 1943). Excluding eclampsia, Eastman and Steptoe (1945) reported a mortality of 0·2 per cent. Dieckmann (1952c) studied the maternal mortality in 12 maternity services in the United States of America during the years 1947-1950. With signs of toxaemia only, the maternal mortality was 0·05 per cent, with symptoms it increased to 0·3 per cent and in eclampsia it rose to 7·3 per cent.

In the present series there were 4 maternal deaths (0·28 per cent). Reference was made to 2 of these deaths in a previous paper (Gibson, 1952). Both might be attributed to the use of bougies for surgical induction of labour and, being wise after the event, both might be considered as preventable deaths. The third patient developed bilateral cortical necrosis after a concealed accidental haemorrhage and the last maternal death was due to sudden cardiac failure on the 5th day of the puerperium. This patient,

TABLE II

Classification of Cases
(Percentage Figures)

	Present Series	Jones (1941)	Dawson (1942)	Dieckmann (1952a)	Eastman (1950a)	Tillmann (1951)
Pre-eclamptic toxaemia	34·3	64	79	44·5	78·1	29·3
Eclampsia	3·1	3·7		2·2	1·2	—
Chronic hypertension	7·5	6·3	20	52·2	20·7	—
Chronic nephritis	1·4	26	1	1·1	—	—
Unclassified	53·7	—	—	—	—	—

a known hypertensive, was admitted to hospital after 5 ante-partum eclamptic fits. Further fits were prevented by the treatment following admission and, after delivery, the patient appeared to be out of danger when cardiac failure supervened. Postmortem examination failed to reveal any satisfactory reason for this unexpected death.

Foetal Mortality

The foetal results are shown in Table III. Some liberty has been taken with the use of the term "stillbirth" because miscarriages have been included under this description. As the miscarriages resulted from toxaemia they must be included if a true assessment of foetal wastage is to be obtained.

Table III
Foetal Results

	Number of Cases	Percentage
Living children	1,275	84·1
Fresh stillbirths	74	10·7
Macerated stillbirths ..	88	
Neonatal deaths	79	5·2
Total births	1,516	—

There were 94 multiple pregnancies in the series including two sets of triplets. The gross foetal wastage was 15·9 per cent. Correction of this figure is of doubtful value—it excludes 53 miscarriages and 19 abnormal babies and provides a corrected foetal mortality of 11·7 per cent. Intrauterine death of the foetus looms large as a problem in toxaemia, a point specifically emphasized by Dienna (1941); it is interesting to note that more than half the stillbirths in the series under review were macerated.

The severity of maternal toxaemia influences foetal mortality just as it influences maternal mortality. Neuweiler (1948) reports a foetal wastage of 26·9 per cent and de Rezende (1951), with a high incidence of eclampsia in his series, had a foetal mortality of 20 per cent. Peckham (1933), including miscarriages, reports a loss of 14·93 per cent. Eastman (1950b) found that the foetal mortality was 21·7 per cent in eclampsia, 6·8 per cent excluding eclampsia and 7·4 per cent in his total series.

Hamilton *et al.* (1949) discussed the effect on foetal mortality of the mode of delivery. They stressed the difficulty of reaching any conclusion because of the multiplicity of variable factors which must be considered in each individual case. No attempt is made to assess the effect of the mode of delivery on foetal mortality in this series. Suffice it to say that labour was surgically induced in 53 per cent of the cases, 20 per cent were delivered with forceps and 12 per cent by Caesarean section. The Caesarean section rate was higher than the hospital average and 70 per cent of the sections were elective.

The Question-Mark in Treatment

According to Brandstrup (1949), Ramsbotham first induced labour for toxaemia in 1832 and, in 1908, Essen-Möller extended the practice of induction as an active prophylaxis against eclampsia.

Gibberd (1931) stated "the cause of albuminuria of pregnancy is pregnancy—the cure is therefore the termination of pregnancy". He advised that induction of labour should be performed early or, at most, within 2 weeks of the onset of toxaemia. His reasons were: (*a*) induction terminated the pregnancy and thus removed the risk of eclampsia, and (*b*) induction reduced the risk of chronic renal damage and of recurrent toxaemia. In this view he was supported by Haultain and Fahmy (1931), Eden and Holland (1931) and Munro Kerr (1933). All considered that continuation of a toxaemic pregnancy for more than 2 weeks was ill-advised and Gibberd (1931) further stated that "if a patient with albuminuria is treated carefully over a long period and induction of labour is performed just soon enough to avoid eclampsia, there is a tendency to regard such treatment as an obstetric triumph made possible by the great clinical acumen of the obstetrician. Actually it is often a grave obstetric blunder in that, as a result of the prolonged albuminuria, an incurable chronic nephritis may develop."

These views influenced the treatment of toxaemia in the Royal Maternity Hospital, Belfast, for many years. However, the foetal

mortality was considerable and prematurity appeared to bear an important relationship to this mortality. The practice of early induction of labour naturally increased the number of premature births and the question was inevitably asked, "Is early induction of labour really essential?"

Theobald (1933) threw considerable doubt upon the contention that toxaemia predisposed to chronic nephritis or to chronic hypertension. His view was supported by Isenhour *et al.* (1942) and Barnes and Browne (1945). Browne (1949), referring to the treatment of toxaemia, stated: "I wish to protest against the prevailing view that, to save a mother from chronic vascular hypertension, labour must be induced prematurely."

These views caused a revision of policy in the Royal Maternity Hospital, Belfast, about the beginning of 1946, i.e., about the beginning of the series under review. Since that date a more conservative approach has been adopted to the treatment of toxaemia, the change being designed to improve the foetal prognosis by reducing the incidence of prematurity. After admission to hospital the patients in the series were kept at rest in bed on a high protein, salt-poor diet with sedatives as required. Progress was assessed daily and the pregnancy was terminated at any time (*a*) if the purpose of conservative treatment, i.e., improvement of the foetal prognosis, was not being served by further continuation of the pregnancy or (*b*) if deterioration in the clinical signs or the occurrence of any symptoms suggested a risk of eclampsia.

Once toxaemia has developed the baby is constantly exposed to the risk of death *in utero*, the result of placental infarction or separation. That this risk is considerable is emphasized by the number of stillbirths that occur in all published series. Dawson (1953) decried conservative treatment of toxaemia because of this complication and urged a return to the practice of early induction of labour. Unfortunately early induction may transfer a prospective stillbirth to the neonatal death column with no improvement in total foetal survival. At what stage in pregnancy does the risk of foetal death *in utero* commence to exceed the risk *ex utero*? In other words, at what stage in pregnancy is the aim of conservative treatment no longer fulfilled by continuation of the pregnancy? To these questions no answer has general acceptance.

Gordon *et al.* (1951), Cosgrove and Chesley (1946, 1948) and Elder (1942) consider that the baby is best served by early induction in all cases of toxaemia. Pomerance (1951) is against conservative treatment after the 34th week of pregnancy. Crosse (1946), giving a paediatric viewpoint, asks that induction of labour before the 35th week of pregnancy should only follow most careful deliberation. Kellar (1950) advocates the 36th week as the optimum time for induction while Browne (1946b) and Baird (1950) try to postpone induction until the end of the 37th week. Balancing the risk of intrauterine death, if pregnancy continues, against the risk of neonatal death, if labour is induced, plays such an important part in the treatment of toxaemia that this wide divergence of published opinion is most disturbing. An analysis of the results in the present series has been undertaken in an effort to provide an answer to this important question.

The Analysis of Foetal Results

The cases have been divided into five groups. This division has been dictated solely by the time in pregnancy at which the patients required admission to hospital because of toxaemia. Each group has been sub-divided—the first subdivision deals with patients delivered less than 7 days after admission, the second 7-14 days and the third subdivision more than 14 days after admission. The number of living and dead babies are shown in each subdivision and the total foetal mortality (stillbirths and neonatal deaths) is expressed as a percentage. When intrauterine death of the foetus occurred the case has been allocated to the subdivision which would correspond to delivery at the time of foetal death. In preparing the analysis 128 cases have been excluded in order to reduce variable factors to a minimum. The exclusions are as follows: (*a*) Multiple pregnancy—94 cases. (*b*) Abnormal babies—16 cases. (*c*) Hydatidiform mole—3 cases. (*d*) Intrauterine death of the foetus—15 cases. Cases of intrauterine death have only been excluded if the baby died before

the patient qualified for inclusion in the series by attendance at the hospital.

The results of the analysis are shown in Table IV. Comparison of the foetal mortality in the five groups shows that there is a progressive decrease in mortality as the maturity of the baby increases, a result which is to be expected. However, the analysis is designed to show the effect of conservative treatment on the foetal prognosis and it is therefore the comparison of foetal mortality in the subdivisions within each group which should be studied. In Groups A, B and C the mortality in subdivision I exceeds, to a striking degree, that in subdivision III. In Groups D and E, the mortality in subdivision I is lower than that in subdivision III—the difference in the percentage mortality is admittedly smaller than in the earlier groups but, as the total number of cases is much increased in the later groups, the difference in mortality between the subdivisions is still significant.

These comparisons indicate that conservative treatment is of undoubted benefit to the baby before the 35th week of pregnancy and that induction of labour should only be performed if the toxaemia is of sufficient severity to endanger the mother. After the 35th week, on the other hand, early delivery gives a better foetal result than does conservative treatment, and induction of labour appears to be the treatment of choice. Indeed, after the 37th week, the foetal mortality is more than doubled by conservative treatment, the relative figures in Table IV being 3·6 per cent after early delivery, and 7·9 per cent after 14 days conservative treatment. If the foetal results are further analyzed, week by week, from the 32nd to the 37th week of pregnancy, the 35th week is the critical stage at which early delivery commences to produce better foetal results than does conservative treatment.

There are certain criticisms of this analysis of foetal results and these must be considered. Firstly, severe cases of toxaemia tend to be treated by induction of labour soon after admission to hospital because an imminent risk of eclampsia precludes any attempt at conservative treatment. The subdivision I in Table IV must contain an abnormal proportion of severe

TABLE IV

Analysis of Foetal Results

Maturity at time of Admission		Subdivision I (0-6 days treatment)	Subdivision II (7-14 days treatment)	Subdivision III (over 14 days treatment)
Group A (under 28 weeks)	Living babies	0	0	7
	Dead babies*	18	9	19
	Mortality (per cent)	100	100	73
Group B (28-31 weeks)	Living babies	3	8	33
	Dead babies*	21	5	19
	Mortality (per cent)	87·5	38·5	36·6
Group C (32-34 weeks)	Living babies	25	22	54
	Dead babies*	16	7	7
	Mortality (per cent)	39	24·1	11·5
Group D (35-37 weeks)	Living babies	157	88	105
	Dead babies*	9	6	11
	Mortality (per cent)	5·4	6·4	9·5
Group E (over 37 weeks)	Living babies	435	120	58
	Dead babies*	16	9	5
	Mortality (per cent)	3·6	6·9	7·9

* "Dead babies" includes stillbirths and neonatal deaths.

cases. Table IV may be amplified by grading the cases in each group and subdivision according to the severity of toxaemia, thus providing 3 separate tables which relate to the three grades of toxaemia, as defined earlier in this paper. The numbers in each subdivision must, of necessity, be disappointingly small after this grading, but the same trend in foetal mortality is still apparent for each grade of severity, except in the group of cases admitted between 35 and 37 weeks. In this group a mild degree of toxaemia is not accompanied by an increase in foetal mortality if conservative treatment is employed instead of early delivery; conversely in moderate and severe cases in this group the advantage of early delivery over conservative treatment is greater than that shown in Table IV.

Secondly, surgical induction of labour may increase the foetal risk and yet, in Table IV, no distinction has been made between cases of spontaneous and induced labour. In order to refute this criticism, 718 cases have been analyzed —in all these cases labour was induced. With the exception of one subdivision, the trend in foetal prognosis among induced cases corresponds to that in Table IV and this suggests that the failure to differentiate between spontaneous and induced labour does not detract from the conclusions which have been drawn from the analysis. The exception occurred in the subdivision dealing with patients who were admitted to hospital after the 37th week and received more than 14 days conservative treatment. The foetal mortality in this subdivision should be 7·9 per cent, but among 21 cases of induced labour there was no foetal mortality. One concludes that this discordant result was due to the small number of cases in the subdivision.

Thirdly, in the preparation of Table IV, no allowance has been made for the age of the patients, their parity or for the type of toxaemia which was present in each case. Browne and Dodds (1940, 1942) and Dieckmann (1952a) stress that the foetal prognosis is worse in chronic hypertension than in pre-eclamptic toxaemia. Dieckmann and Kramer (1942) refers to the lethal effect of albuminuria and chronic nephritis on the foetus. Unfortunately these criticisms must go unanswered. Analysis of the cases by age or parity so reduces the number of cases in each subdivision that interpretation is impossible and a failure to classify 53·7 per cent of the cases in the series prevents an assessment of the foetal mortality for each individual disease.

The Maternal Risks of Conservative Treatment

There were 658 patients in the total series who received more than 7 days conservative treatment in hospital before delivery. During treatment the toxaemia increased in 121 cases (18 per cent) and eclampsia occurred in 8 cases. If one admits that eclampsia is always a preventable disease these cases are hard to justify and must be attributed to faulty management. However, in each case, the fits occurred during labour or after delivery. Experience has shown that these types of eclampsia occur with less warning than the ante-partum type, that they are difficult to exclude by preventive treatment and that they have a better prognosis. Among the remaining 762 cases in the series there were 20 cases of intra-partum or post-partum eclampsia. This higher incidence could, but should not, be taken to indicate that early delivery increases the risk of eclampsia.

Toxic accidental haemorrhage is the other risk to which patients may be exposed during the conservative treatment of toxaemia. That this risk is very small is shown by the occurrence of only 5 cases in the conservative series—all were mild and did not give rise to anxiety.

Conservative treatment of toxaemia must be carried out in hospital under constant supervision and warning signs of increasing severity must not be ignored. With this important proviso, conservative treatment does not appear to increase the immediate maternal risk. As to the late effects of conservative treatment no opinion is expressed—a survey of all the cases in this series is almost complete and the results of this survey will be published at a later date.

Discussion

Acceptance of the general concept, that continuation of a toxaemic pregnancy does not lead to late maternal sequelae, has become widespread and conservative treatment of toxaemia is frequently employed. Personal experience

during 5 years of close association with the problem in the Royal Maternity Hospital, Belfast, suggested that all was not well with this conservative approach and that babies were being lost because of it. The papers of Irving (1939, 1941) stimulated the writer to analyze the cases of which he had had experience and this analysis has been described.

The analysis shows that, until the 35th week of pregnancy, conservative treatment is of benefit to the baby and confirms that the present practice is beneficial. It also shows that, after the 35th week, early delivery gives better foetal results and that conservative treatment, though adopted to improve foetal results, is detrimental to the baby. The concept of a critical stage in pregnancy beyond which active intervention is beneficial, is not new to obstetric practice; a critical week is recognized in the treatment of diabetes and of placenta praevia.

There is a tendency to postpone the active treatment of toxaemia from day to day. This temporization has little value—it requires weeks rather than days to alter, to a material degree, the birthweight of the baby. This tendency is particularly common if the baby is small for the period of gestation but, as the size of the baby reflects the poor function of the placenta, intrauterine death of the foetus is a frequent outcome. Weight for weight, the premature "toxaemic" baby seems to stand a better chance of neonatal survival than the normal premature baby and, if the maturity of the baby is known to be correct, its smallness should act as an added incentive to expedite delivery.

Surgical induction of labour will frequently be employed if conservative treatment of toxaemia is to be abolished after the 35th week of pregnancy. This operation is not devoid of risk to the mother and to the baby. The effectiveness, and therefore the safety, of induction of labour depends largely on the state of the cervix at the time of induction. If the cervix is "ripe" induction is easy and effective, the risks are minimal and the results are good. Should labour be induced after the 35th week of pregnancy even if the cervix is "unripe" and unsuitable for induction? The answer to this question must depend on the attitude which one adopts to Caesarean section. In a previous paper (Gibson, 1952), the problem of difficult induction of labour was discussed and certain recommendations were made. Firstly, a difficult induction should only be undertaken if there was a strong indication for the termination of pregnancy. Secondly, rupture of the membranes was the safest method to employ in such cases. Thirdly, the foetal mortality rose if there was a prolongation of the latent interval before the onset of labour—this mortality was negligible until 72 hours had elapsed and then the foetal risk increased steadily. Fourthly, Caesarean section should be considered seriously if labour had not ensued 72 hours after induction, the indication being the foetal risk associated with further prolongation of the latent interval.

To answer the question which has been posed, the writer considers that moderate and severe cases of toxaemia, which occur after the 35th week of pregnancy, do provide a strong indication for induction even if the cervix is unsuitable. Though condemning temporization in general, he feels that it has a place in the treatment of mild cases of toxaemia particularly before the 38th week of pregnancy. Analysis showed that, in mild cases, the foetal results after conservative treatment were comparable to those after early delivery and, this being the case, delay is justified until the cervix becomes suitable for induction of labour.

Summary

1. 1,420 cases of toxaemia of late pregnancy were investigated.

2. There were 4 maternal deaths in this series, an incidence of 0·28 per cent.

3. The gross foetal mortality was 15·9 per cent. If abnormal babies and miscarriages were excluded, the foetal wastage was reduced to 11·7 per cent.

4. The foetal results were analyzed to show the effect of early delivery and of conservative treatment.

5. This analysis demonstrated that the 35th week of pregnancy should be considered the critical week. Before the 35th week conservative treatment improved the foetal prognosis and after the 35th week early delivery gave better results.

6. With adequate safeguards, conservative

treatment did not increase the immediate maternal risks.

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THE TREATMENT OF HYDRAMNIOS COMPLICATED BY ANENCEPHALY

A Comparison of Methods

BY

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WHEN a diagnosis of hydramnios is made antenatally and the presence of gross foetal abnormality such as anencephaly is found, the obstetrician in charge has the choice of two forms of treatment. He may adopt a waiting attitude and not interfere with the pregnancy or he may follow a more active regime and induce labour prematurely. Though most obstetricians favour the latter there are some who have believed the conservative approach is to be preferred. This short paper is the result of an investigation designed and carried out with the hope of getting a clear answer to this uncertainty.

Method. The investigation which has taken the form of a review of treated cases was only possible because it was known that the practice in the Simpson Memorial Maternity Pavilion, Edinburgh, in regard to the management of cases of hydramnios and anencephaly differed from time to time from that in Sheffield. Cases of hydramnios and anencephaly treated in these two towns were therefore reviewed by one of us (T.M.A.), in the hope that a valid comparison could be made between two different lines of treatment, and that useful information would result. Two hundred and one individual case records were carefully scrutinized and details relevant to the proposed study recorded. Punch cards were used to facilitate subsequent analysis. Of the 201 cases studied, 77 had been treated in the Jessop Hospital for Women, Sheffield, and 27 in the City General Hospital, Sheffield, and 97 in the Simpson Memorial Maternity Pavilion, Edinburgh.

Results. Labour had been induced prematurely (before the 38th week) in 111 cases, whereas in the remaining 90 cases it had not been induced prematurely. Of the 111 cases, however, only 93 had had a surgical induction, and it was felt that this smaller number actively treated should be preferred to the larger number. Of the 90 cases whose labours were not induced prematurely 30 had been admitted to hospital as emergencies in labour, and it was felt that a better comparison would result if these 30 cases were omitted. Of the remaining 60 cases, 5 had been given one or more medical inductions near or after term, but as these inductions were apparently given for post-maturity or niggling labour rather than for the hydramnios and anencephaly it is felt that these cases may be retained in the conservative treatment group. The substance of this paper, therefore, is a comparison between two groups of cases which for convenience may be called the Surgical Induction Group (93 cases), and the Conservative Treatment Group (60 cases). In the former, artificial rupture of the membranes had been performed before the 38th week of pregnancy; in the latter, no surgical induction was performed though, as already stated, one or more medical inductions were given at or after term in 5 cases.

Firstly, the two groups were examined in respect of age of patient, parity, rate of onset of hydramnios, and history of previous obstetrical

abnormality. The similarity of the two groups in these four respects was sufficiently close (Tables I-IV) to make comparison of the results of treatment valid.

TABLE I
The Age Distribution

Age	Surgical Induction Group (93 cases)	Conservative Treatment Group (60 cases)
–24	28	24
25–34	49	28
35–	16	8

TABLE II
The Parity Distribution

Parity	Surgical Induction Group (93 cases)	Conservative Treatment Group (60 cases)
1	46	34
2–4	38	22
5–	9	4

TABLE III
The Rate of Development of Hydramnios

Rate of Onset of Hydramnios	Surgical Induction Group (93 cases)	Conservative Treatment Group (60 cases)
Rapid ..	6	2
Moderate ..	19	12
Slow	40	24
Unknown ..	28	22

TABLE IV
The History of Previous Obstetrical Abnormality

Previous Obstetrical Abnormality	Surgical Induction Group (93 cases)	Conservative Treatment Group (60 cases)
Previous Ante-partum Haemorrhage	5	4
Previous Post-partum Haemorrhage	5	3
Previous Abortion ..	15	9
Previous Toxaemia ..	7	5
None	69	47

Next, the diagnosis-delivery interval was examined and immediately the main difference between the two groups was apparent. Whereas in the Surgical Induction group all cases were delivered within a fortnight of diagnosis, in the Conservative Treatment group 48 of the cases were not delivered for at least a fortnight after diagnosis (Table V). Clearly, therefore, the

TABLE V
The Diagnosis-Delivery Interval

Diagnosis-Delivery Interval in Days	Surgical Induction Group (93 cases)	Conservative Treatment Group (60 cases)
–6 ..	58	5
7–13 ..	35	7
14–20 ..	—	18
21–27 ..	—	13
28+ ..	—	17

patients in the Surgical Induction group had the advantage of getting rid of a useless gestation more quickly. The conservative treatment was, however, also remarkably effective as in all but 14 cases spontaneous labour ensued by the 38th week (Table VI). If the 30 cases admitted as emergencies in labour are also included, the

TABLE VI
The Duration of Amenorrhoea at Onset of Labour

Weeks	Surgical Induction Group (93 cases)	Conservative Treatment Group (60 cases)
–32 ..	26	10
33–35 ..	38	14
36–38 ..	29	22
39–41 ..	—	11
42+ ..	—	3

incidence of spontaneous labour before the 39th week was 72 out of 90 cases. Conservative treatment was not, however, without risk, as the following brief case record illustrates.

Mrs. K.M., aged 36 and gravida-2, gave a history of having had an upper segment Caesarean section on account of toxaemia and contracted pelvis. In the present pregnancy hydramnios and anencephaly were diagnosed at the 30th week of pregnancy; conservative treatment was practised until the 34th week when she was admitted to hospital with a ruptured uterus. After hysterectomy she made an uneventful recovery.

The two groups were then compared as regards the complications that might have resulted from one or other method of treatment. The length of labour was similar in the two groups as was the frequency of ante-partum and post-partum haemorrhage (Tables VII and VIII).

TABLE VII
The Duration of Labour

Durations of Labour in Hours	Surgical Induction Group (93 cases)	Conservative Treatment Group (60 cases). 59+1*
–11 ..	61	36+1*
12–23 ..	24	18
24–47 ..	6	2
48– ..	2	3

* One case of hysterectomy.

TABLE VIII
The Incidence of Pregnancy and Labour Abnormality

Pregnancy and Labour Abnormality	Surgical Induction Group (93 cases)	Conservative Treatment Group (60 cases)
Ante-partum Haemorrhage	10	6
Post-partum Haemorrhage	7	4
Notifiable Puerperal Pyrexia	9	4

Notifiable puerperal pyrexial was rather commoner in the Surgical Induction group (Table VIII) but, as the infection was extragenital in 3 cases, compared with only 1 case of extragenital infection in the conservative treatment group the difference should not be given much weight. In contrast the incidence of operative interference for the delivery was rather commoner in the Conservative Treatment group, (13 per cent) than in the Surgical Induction group (5 per cent, Table IX). Of the 3 cases in which cleidotomy was required, 2 occurred in this Conservative Treatment group, and it was in this group that there occurred the major complication of uterine rupture already described.

The Surgical Induction group was then examined separately in respect of the induction-delivery interval (Table X). Of the 93 cases in this group it is interesting that in all but 6 of them delivery was complete within 72 hours of the induction; in these 6 cases no harm resulted from the delay because all were delivered within a further 18 hours. The induction-delivery interval when studied in relation to the duration of amenorrhoea at the onset of labour showed a higher incidence of delay in delivery when the amenorrhoea was under 32 weeks—as might be expected (Table XI).

TABLE IX
The Incidence of Operative Interference ($P<0{\cdot}1$)

	Surgical Induction Group (93 cases)	Conservative Treatment Group (60 cases)
Operative Interference for delivery	5 (5 per cent)	8 (13 per cent)
No interference	88	52

TABLE X
The Distribution of the Surgical Induction-Delivery Interval

Surgical Induction-Delivery Interval in Hours ..	–11	12–23	24–47	48–71	72+
Cases	30	31	15	11	6

TABLE XI
Induction-Delivery Interval in Relation to Duration of Pregnancy

Induction-Delivery Interval	–32 weeks	33–35 weeks	36–38 weeks	Total
–23 hours	14	26	21	61
24– hours	12	12	8	32

SUMMARY

Two hundred and one cases of anencephaly and hydramnios have been reviewed.

A comparison has been made between a group of 93 cases treated by rupture of the membranes before the 38th week of pregnancy, and a group of 60 cases allowed to go into labour spontaneously. These two groups were comparable in respect of age, parity, rate of onset of hydramnios, and history of previous obstetric abnormality.

Treatment by artificial rupture of the membranes had the clear advantage that it shortened a useless gestation, presumably with benefit to the mother; it also led to a small reduction in the incidence of labour difficulties of such a degree as to require operative interference. In 87 out of the 93 cases the induction-delivery interval was less than 72 hours: and all the remaining 6 cases were delivered within a further 18 hours. The surgical induction was sometimes less rapid in effect if carried out before the 32nd week of pregnancy.

Though in the Conservative Treatment group premature spontaneous labour generally ensued this treatment was in no respect demonstrably superior to treatment by artificial rupture of the membranes.

Conclusion

As a working rule, the association of anencephaly and hydramnios should be treated by artificial rupture of the membranes as soon as a diagnosis is made, with the possible exception of cases diagnosed before the 32nd week of pregnancy.

We thank the Consultant staffs of the hospitals concerned for their permission to publish this review of cases under their care.

THE TREATMENT OF TUBERCULOUS ENDOMETRITIS WITH STREPTOMYCIN AND PAS*

BY

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THIS report analyzes the results which have so far been obtained in a controlled trial of the treatment of tuberculosis of the endometrium with streptomycin and para-aminosalicylic acid. The investigation is being conducted by a Joint Sub-Committee representing the Royal College of Obstetricians and Gynaecologists and the Research Committee of the British Tuberculosis Association, and was started in July, 1950. The centres in which the cases in this trial have been studied are in Birmingham, Edinburgh, Exeter, Glasgow, London and Oxford.

When this investigation was being planned, it was decided that the best way to ascertain the value of streptomycin and PAS in the treatment of tuberculous endometritis would be in the form of a controlled trial. At that time, previous experience did not suggest that to withhold treatment was likely to involve any appreciable risk to the patient in most cases.

It was accordingly agreed to include control cases under the following conditions:

(1) All control patients whose disease was still active at the end of an observation period of one year should receive the full course of treatment.

(2) All control cases showing any clinical deterioration should be withdrawn from the trial and treated at once.

(3) All cases in which it was felt that it might be harmful to withhold treatment should be excluded from the trial and treated at once.

At the outset, it was agreed that the cases included in this trial should be restricted to examples of proved endometrial tuberculosis, irrespective of the presence or absence of tubo-ovarian masses. Before inclusion in the series, each patient was examined by a chest physician, the chest was X-rayed and a catheter specimen of urine was obtained for guinea-pig inoculation. No patient who was found to have any type of active extra-genital tuberculosis was included in the trial.

When a patient was found to be suitable for the investigation, particulars of her case were sent to Dr. Ian Sutherland, who is responsible for the statistical aspects of the investigation. He allocated each case either to a "Treatment" or to a "Control" group, from pre-arranged lists based upon random sampling numbers.

PRESENT SERIES

The total number of cases originally admitted to the trial was 126, but for various reasons it has been found necessary to exclude 17 of these from the present analysis. In 4 instances (2 treatment, 2 control), forms were not received from the centre concerned and in 9 (6 treatment, 3 control) the information supplied was inadequate. A further 3 patients (all control) were later

* A preliminary report of a Joint Sub-Committee representing The Royal College of Obstetricians and Gynaecologists and The Research Committee of the British Tuberculosis Association. The Sub-Committee consisted of: Dr. A. M. Sutherland (Chairman), Miss J. Barnes, Miss A. M. Bigby, Mr. J. B. Blaikley, Mr. R. A. Brews, Professor J. C. M. Browne, Dr. W. D. A. Callam, Dr. W. J. Clegg, Dr. A. D. T. Govan, Dr. M. Haines, Dr. A. S. Hall, Professor F. R. G. Heaf, Miss G. Hill, Dr. J. V. Hurford, Mr. I. M. Jackson, Dr. M. Jackson, Dr. A. M. C. Macpherson, Dr. G. P. Maher-Loughnan, Mr. J. D. Murdoch, Mr. L. B. Patrick, Mr. C. D. Read, Dr. R. W. Riddell, Dr. J. G. Scadding, Miss D. M. Shotton, Mr. J. A. Stallworthy, Mr. D. M. Stern, Dr. I. Sutherland (Statistical Adviser), Dr. R. L. Vollum.

found to have a tuberculous infection of the urinary tract and the last patient (treatment group) had an active pulmonary lesion and was included in the trial in error. Of the 126 patients, 78 were contributed by the Glasgow centre, 16 by the Oxford centre, 11 by the Birmingham centre, 9 by the London centre, 6 by the Edinburgh centre and 6 by the Exeter centre.

Clinical Features. The findings in this paper are based on a study of the remaining 109 cases and brief reference will first be made to certain clinical features of this group. The average age was 28 years, the youngest patient being aged 16 years and the oldest 48. Seventeen patients were single, 90 were married and the remaining 2 were widows. Only 9 patients gave a history of previous pregnancy, 3 having had one or more full-time pregnancies, 4, one or more miscarriages, and 1, two full-time pregnancies and one miscarriage.

In the space available, it will not be possible to discuss the symptomatology of these cases in any detail, so that attention will be confined to the principal complaint in each case. Infertility was the most common presenting symptom and occurred in 52 instances. Twenty-one patients complained of pain of various types, usually situated in the lower abdomen, and profuse and sometimes irregular menstruation was found in 12 cases. Ten patients complained of amenorrhoea, which was usually secondary in type, and profuse vaginal discharge occurred twice. The occurrence of amenorrhoea in a relatively small proportion of cases emphasizes the present view that this symptom is much less frequent than many earlier publications indicated. No complaint was recorded in 3 of the case records, the space being left blank, and the remaining 9 made no complaint of any kind although there was a previous history of some type of tuberculous infection. The presenting symptoms of the patients in the trial are shown in Table I.

X-ray examination of the chest revealed a presumably quiescent tuberculous pulmonary lesion in 32 cases, the remainder showing no abnormality of any kind. On vaginal examination the pelvic organs were found to be essentially normal in 61 instances. In 47 cases, a variable degree of adnexal thickening was discovered, the condition being bilateral in the majority. In 1 case, the condition of the pelvic organs was not mentioned in the case record.

Diagnosis. A provisional diagnosis of endometrial tuberculosis was based initially on the histological findings in the curettings, but bacteriological proof was sought in every case and a positive result was found in 75 of the 109 cases. In several additional cases the bacteriological results are still awaited, or are omitted from the records. It is considered that the very small amount of tissue obtained by curettage in many instances may be the main reason for the rather high number of negative results.

Bacteriology. In many of the cases with positive bacteriology an attempt was made to type the organism. This was successful in 56 instances, the tubercle bacilli being of the human type in 52 cases and of the bovine variety in the remaining 4. Sensitivity of the organism to streptomycin has been tested in 59 cases. In 58 the organism was found to be streptomycin-sensitive, though in 7 cases the sensitivity was only partial and in the remaining instance the organism was streptomycin-resistant.

TABLE I

Presenting Symptoms of Patients in Trial

	Total Patients	Infertility	Pain	Bleeding	Amenorrhoea	Vaginal Discharge	None	No Record
Treated	57	26	11	7	5	0	6	2
Control	52	26	10	5	5	2	3	1
Total	109	52	21	12	10	2	9	3

Management

"Treatment" Group. As has already been mentioned, following the initial diagnosis, each case was allocated either to the "Treatment" or to the "Control" group. The cases in the "Treatment" group were given 1 gramme of the calcium chloride complex of streptomycin daily by intramuscular injection for 84 consecutive days and 3 grammes of PAS (sodium salt) 4 times daily by mouth, over the same period. All patients were ambulant throughout treatment and many continued in their jobs. The treatment was given either at the out-patient department of the hospital or under the supervision of the family doctor, depending on circumstances.

An attempt has been made to assess the progress of the condition by carrying out examination of the endometrium at regular intervals and this was done in one of two ways. The first of these was endometrial biopsy, which is essentially an out-patient procedure, does not require anaesthesia as a rule and is virtually painless. A special biopsy curette is employed for the purpose and the amount of tissue obtained is usually small. The second was dilatation of the cervix followed by curettage, which is carried out under general anaesthesia and necessitates a short stay in hospital. This latter procedure is associated with certain risks in the presence of active endometrial tuberculosis and is usually employed only after at least 2 consecutive negative endometrial biopsies. An advantage of full curettage is that it yields a larger amount of tissue than endometrial biopsy and thus the chance of discovering tubercle bacilli, if present, is increased.

Whenever possible, endometrial biopsy was performed halfway through treatment, at the end of treatment, 3 months after treatment and 6 months after treatment. At the end of a year from the commencement of treatment, dilatation of the cervix and full curettage were carried out. In every case in which it was feasible these examinations were made in the premenstrual phase of the menstrual cycle, as at this time there is the best chance of obtaining a positive result in those cases in which the infection is still present. Part of the tissue obtained on each occasion was used for histological examination and the remainder for bacteriological investigation.

"Control" Group. In the "Control" group of cases, no active treatment of any kind was carried out. These patients were kept under observation and reported regularly. Whenever possible, endometrial biopsy was done at the same intervals as in the "Treatment" group. Full curettage under anaesthesia at the end of a year of follow-up was rarely required, however, as endometrial biopsy was usually sufficient to demonstrate that the infection was still present. As has been mentioned previously, all patients in this category were removed from the trial and treated at once if they showed any evidence of clinical deterioration and all patients still positive at the end of a year were given a full course of treatment.

Results of Follow-up

(1) *"Treatment" Group.* There were 57 cases in this category. In 8 of these no follow-up is available, either because the patient has not yet completed treatment or because treatment was refused. In 4 further instances it was found necessary to discontinue treatment before the completion of the course, and all 4 patients were subsequently removed from the trial. Two patients developed slight vestibular disturbance after 22 and 52 grammes of streptomycin respectively but in each case the symptoms gradually cleared up following the cessation of treatment. One patient developed a generalized reaction associated with swelling of the face, headaches, pains in other parts of the body and malaise. Treatment was stopped and the condition subsided rapidly. Resumption of the streptomycin injections caused no upset but the symptoms recurred when PAS was again administered. The PAS was stopped and isoniazid was substituted, the patient being removed from the trial in consequence. The fourth patient had a severe generalized skin eruption, with loss of most of the hair from her scalp, after 22 grammes of streptomycin. When treatment was stopped, the skin condition rapidly subsided and her hair has now returned to normal. In this case streptomycin was found to be the drug responsible for the severe reaction.

In 27 cases the follow-up of 1 year has been completed. In 24 of these (89 per cent) there has

been no further evidence of endometrial tuberculosis, while the condition has recurred in the remaining 3 patients. In all 3 the endometrium was negative for a time after treatment and the tuberculous condition recurred towards the end of the follow-up period. At this point it seems worthy of mention that the organism was typed in 2 of these 3 cases, one being human and the other bovine. In both instances the organisms were found to be sensitive to streptomycin. In 18 further cases a partial follow-up is available, and in all of these there has so far been no evidence of recurrence. While the latter results provide additional evidence of the value of streptomycin and PAS, they must be interpreted with some caution, as recurrence apparently does not occur during or immediately after treatment.

The effect of treatment on the adnexal masses which were present in many instances was very variable. In some cases the masses were no longer palpable and in many others they were reduced in size. In a few patients there was no apparent change in these swellings. It is not always possible without laparotomy to obtain accurate information regarding the response of associated adnexal masses to treatment and one can only speculate as to how many of them clear up along with the endometrial infection. It is worthy of mention that, of the 3 patients who showed recurrence of infection after treatment, only 1 had palpable swellings in the tubo-ovarian regions. Radiological control by salpingography with water soluble media was used in a few cases in certain centres, but not as a routine.

(2) "*Control*" *Group*. There were 52 cases in this category. In 3 of these no follow-up is available, either because the patient is not yet due to report or because further attendance was refused. In no less than 10 further cases there was clinical deterioration which necessitated removal from the trial and immediate treatment before the end of the year of control. In 8 of these patients there was evidence of pelvic flare-up of the tuberculous condition, as shown by the development or extension of tubo-ovarian masses and by the occurrence of pain which was sometimes fairly severe. In a further instance a previously quiescent chest lesion became active, and the tenth patient developed tuberculous meningitis. The last patient received a prolonged course of streptomycin and PAS in another hospital and has made a very good recovery. It is thus apparent that an appreciable number of cases of tuberculous endometritis show clinical deterioration if untreated. There was no evidence of any comparable worsening of the clinical condition of any of the treated cases.

In 25 cases the follow-up of 1 year has been completed. The endometrium still showed evidence of tuberculous infection in 20 of these and was negative after full curettage in the remaining 5 (20 per cent). In many of the cases in which the endometrium was positive at the end of a year of follow-up, one or more intermediate specimens had been negative. It thus appears that the initial full curettage may, even in the absence of treatment, be followed by a period in which the endometrium on biopsy shows no evidence of tuberculosis. In 14 further cases a partial follow-up is available. The endometrium was positive in 6 of these and negative in the other 8, but it is possible that the results at the end of a year may show a higher incidence of positive cases.

The results 6 months and 1 year after entry to the trial are shown in Tables II and III.

TABLE II

Results Six Months after Entry to Trial

	Total Patients with Examination of Endometrium after 6 Months	Endometrium Positive	Endometrium Negative	Percentage Negative
Treated	26	1	25	96
Control	27	12	15	56

TABLE III

Results One Year after Entry to Trial

	Total Patients so far Followed up for One Year	Endometrium Positive	Endometrium Negative	Percentage Negative
Treated	27	3	24	89
Control	25	20	5	20

RELATIONSHIP BETWEEN RESULTS AND BACTERIOLOGY

With reference to the diagnosis of endometrial tuberculosis, it must be appreciated that a certain number of cases based on histological findings alone have been included in the above analysis. It seems reasonable to include such cases and that bacteriological confirmation is desirable but not essential. In order to clarify this point, the results have been worked out in the "Treatment" and "Control" groups after excluding all cases in which bacteriological proof of the tuberculous nature of the lesion was not available.

In the "Treatment" group there were 31 bacteriologically proved cases which had been followed up. Twenty-one of these had completed a year of follow-up, 18 (86 per cent) remaining negative and the other 3 showing recurrence. In 10 further cases the follow-up was incomplete, all 10 remaining negative. There were 26 "Control" cases in which bacteriological proof had been obtained and in which a follow-up was available. Eighteen of these had been followed up for a full year, only 2 (11 per cent) being negative. A partial follow-up is available in 8 further cases, 4 being positive and 4 negative. It will thus be seen that the figures obtained for the bacteriologically-proved cases are in close agreement with those for the whole series.

The results in the cases in which no bacteriological proof was obtained are also of interest. Of the 12 control cases in this category, 5 were still positive at some time during the follow-up whereas all 13 cases in the treated group remained negative throughout. When taken in conjunction with the histological findings, these results are consistent with the assumption that the lesions in these cases are probably tuberculous in nature. The results 6 months and 1 year after entry to the trial according to the nature of the diagnosis are shown in Tables IV and V.

RESULTS OF TREATMENT IN RELATION TO SYMPTOMATOLOGY

By far the commonest primary complaint in the treated cases was infertility, which was present 21 times. None of these patients has so far become pregnant and, while this is disappointing, it is not at all surprising. Examples of pregnancy occurring in patients with a history of proved endometrial tuberculosis are extremely rare in the literature. It is likely that this fact is related to the high incidence of blockage or morbidity of the Fallopian tubes in such patients. While treatment may arrest the active infection,

TABLE IV

Results Six Months after Entry to Trial according to Nature of Diagnosis

Diagnosis		Total Patients with Examination of Endometrium after 6 Months	Endometrium Positive	Endometrium Negative
Treated	Bacteriological	19	1	18
	Histological only	7	0	7
Control	Bacteriological	19	12	7
	Histological only	8	0	8

TABLE V

Results One Year after Entry to Trial according to Nature of Diagnosis

	Diagnosis	Total Patients so far Followed up for One Year	Endometrium Positive	Endometrium Negative
Treated	Bacteriological	21	3	18
	Histological only	6	0	6
Control	Bacteriological	18	16	2
	Histological only	7	4	3

the disorganization of tubal structure which has already occurred may be such that normal function cannot be restored.

The results of treatment in relation to the remaining complaints were generally satisfactory. All 9 patients complaining principally of abdominal pain reported either complete relief or considerable improvement after treatment, and the 6 patients with profuse and usually irregular menstruation all reported a return to a normal menstrual cycle. There were 3 cases of amenorrhoea in this category and all 3 reported the onset of normal periods, including one patient aged 24 who had never menstruated previously.

DISCUSSION

When considering the results of treatment of endometrial tuberculosis with streptomycin and PAS, it is apparent that the results so far obtained are better than those observed in the controls as judged on the basis of a 12 months' follow-up. The occurrence of toxic manifestations in 4 patients during treatment is disturbing, although in no case were there any permanent ill effects. In future, it is hoped to reduce the incidence of such toxic reactions by using streptomycin sulphate instead of the calcium chloride complex.

As far as the control cases are concerned, although an appreciable number did become negative without treatment, the results obtained show that one is not now justified in withholding treatment from any patient with proved tuberculosis of the endometrium. The main reasons for this conclusion are the fact that the majority of cases in the control group remained positive on follow-up and the fact that a substantial number showed clinical deterioration in the course of the trial and required immediate treatment.

In closing, it appears worthy of mention that a new trial was started recently in which streptomycin and PAS are being compared with streptomycin and isoniazid. Nineteen cases have so far been included in the former category and 24 in the latter. At present it is too early to make any statement regarding the relative value of these drug combinations.

SUMMARY

An analysis has been made of the results so far obtained in a controlled trial of streptomycin and PAS in the treatment of tuberculosis of the endometrium. All patients with any type of active extra-genital tuberculosis were excluded from the investigation. Of the 109 patients in the trial, 57 chosen at random were treated and the remaining 52 were allocated to a control group.

In 4 cases, treatment had to be discontinued before completion of the course because of toxic manifestations. Twenty-seven treated patients were followed up for 1 year and only 3 showed evidence of recurrence. In other 18 cases, the follow-up after treatment was under 1 year and all 18 have so far remained negative.

Ten control cases had to be removed from the trial because of clinical deterioration and required immediate treatment. Twenty-five were followed up for 1 year and in 20 the endometrium still showed evidence of tuberculosis. In 14 further cases a shorter follow-up was available, the endometrium being positive in 6 of these patients and negative in 8.

It is considered that the results so far obtained appear to indicate the use of streptomycin and PAS in patients with proved endometrial tuberculosis.

AMNIOTIC EMBOLISM

A Report of Two Fatalities

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SINCE Steiner and Lushbaugh (1941) first described pulmonary embolism of amniotic fluid as a cause of sudden death in pregnancy, at least 40 instances of the condition have been recorded. Four cases have recently been added by Sluder and Lock (1952) who review the literature and discuss the aetiology of the condition. Shotton and Taylor (1949) have recorded 1 case in this country. It is thought worth while to record 2 further cases occurring recently in Leeds, as personal discussion with obstetricians and pathologists has suggested that many are still unaware of the condition; in addition the second of the 2 cases presented certain unusual features which made the establishment of the diagnosis a matter of some difficulty. Since these came to notice we have been consulted about 2 more deaths in which the circumstances were probably those of amniotic embolism, but we had no opportunity to prove it.

CASE REPORTS

Case 1. Mrs. G.N., aged 29, was admitted to hospital in labour. Her previous 2 pregnancies had resulted in the spontaneous delivery of a premature infant, 5 years previously, and of a full-time infant, 3 years previously. She had reached term in this, her 3rd pregnancy.

Twice during the present pregnancy she had been admitted to hospital, on the first occasion with a threatened abortion at 6-months gestation, and on the second as a case of ante-partum haemorrhage at the 8th month. On this latter occasion inspection of the cervix had excluded any local cause for bleeding, and X-ray examination suggested an upper segment implantation of the placenta. In the absence of signs of toxaemia or of recurrence of the bleeding, the patient was discharged after a few days.

Physical examination on her last admission revealed no obvious abnormality. There was no oedema. Her blood pressure was 120 systolic, 75 diastolic. The infant was lying longitudinally in the left occipito-lateral position, the head being free. The foetal heart sounds were satisfactory. Labour was not well established, the patient having had irregular backache and a "show". No history of ruptured membranes was given and no liquor was seen.

Sleep was induced with Nembutal gr. 3, and 3½ hours later the patient awoke with a desire to pass urine. She complained of feeling "shaky", and, as her bladder still appeared full after micturition, she was catheterized. During this operation she complained of nausea. She then had a fit, characterized by a short phase of tonic movements followed by coma. The patient, though breathing regularly, became deeply cyanosed, and this was not relieved by oxygen. The pulse was imperceptible at the wrist, and soon the respirations became shallow and irregular, and then ceased altogether. She died 25 minutes after waking.

An autopsy was performed (by W.G.) 8 hours after death. The body was that of a well-nourished female subject. The features were congested. The protuberant abdomen suggested advanced pregnancy.

The brain weighed 1,500 g. A small area of subarachnoid haemorrhage was present over the right cerebral hemisphere. The blood was not clotted, and

escaped when the membranes were incised. There was no other obvious abnormality.

Numerous small submucosal haemorrhages were present in the stomach.

The lungs were congested and moderately oedematous.

The heart weighed 300 g. The right chambers were moderately dilated. A small area of sub-endocardial haemorrhage was present in the left ventricle below the aortic cusps. No clotted blood was seen, either in the heart or great vessels.

The uterus contained a mature normal female foetus weighing 6 pounds 6 ounces (2,900 g.). The membranes were ruptured and closely applied to the foetus. The placenta was in the upper segment of the uterus and had commenced to separate.

Other organs were anatomically normal.

Histology

Sections examined from 6 different parts of the lungs showed many medium-sized and small branches of the pulmonary artery to be blocked by masses of pink-staining stringy material and epithelial squames (Fig. 1). Similar material was present in many arterioles (Fig. 2). In a number of vessels lanugo hairs with well-marked melanin granules were seen in cross section (Fig. 3). The foreign material stained with mucicarmine, but did not stain for fat. It was seen in all the sections of lung examined and, it seemed, at least one-third of all arteries and capillaries were affected. The lung parenchyma in relation to the affected vessels was congested and oedematous, but there was no inflammatory reaction.

Sections from pituitary, brain, heart muscle, spleen, liver, kidneys, pancreas, thyroid, adrenals and placenta were also examined: in none of them was any abnormality detected, and no foreign material was identified in vessels.

The histological findings in the lung left no doubt that death was due to pulmonary embolism of amniotic contents.

Case 2. A married woman, 23 years of age, had reached the 8th month in her second pregnancy. Her first pregnancy had been normal and the child was now 13 months old. Until the day of her death, this 2nd pregnancy had been uneventful. On the morning of that day she had frequency of micturition. That evening she suddenly sat up in bed and complained of severe pain in her stomach. She quickly became unconscious and died within a few minutes.

An autopsy was performed (by C.P.) the following day. The body was that of a well-nourished young female in an advanced stage of pregnancy.

The brain, which weighed 1,200 g., was slightly oedematous.

The heart weighed 230 g. There was some terminal dilatation of the right ventricle. All the chambers and the great vessels contained dark fluid blood.

The trachea and bronchi contained a little foamy exudate. Both lungs were collapsed for the most part, and of a dark purple colour except in the anterior borders where they were pinkish and somewhat over-distended. On section the lower lobes were congested: there was no visible oedema.

The uterus contained a normal female foetus 5 pounds 2 ounces (2,460 g.) in weight. The head of the foetus was about to engage the pelvic brim. The amniotic sac had ruptured, there being an almost vertical tear in the posterior wall about 15 cm. in length. The placenta was attached to the right posterior aspect of the uterus and had become detached over a distance of about 5 cm. in its lower part.

Other organs were anatomically normal.

Histology

Lungs: Haematoxylin and eosin-stained sections were examined from many areas of the lungs. In two small vessels tiny pieces of pink stringy material were seen, but the appearances were not conclusive. In frozen sections stained for fat, however, much granular fatty material was seen lying free in large and small branches of the pulmonary artery and in the capillaries of the alveolar walls; some small vessels were apparently blocked by this foreign material (Fig. 4). The foreign material did not stain with mucicarmine. There was considerable oedema of the lungs, especially of the lower lobes.

Sections from all other organs were normal.

A drop of amniotic fluid taken from the uterus was found to contain much granular material of a fatty nature which stained with Scharlach R.

A diagnosis of amniotic embolism was made on the history and the finding of fatty material in the pulmonary vessels.

Discussion

From a clinical point of view the first case resembles closely those previously described. The occurrence of acute respiratory failure during an uneventful labour in an apparently healthy multipara has been a common feature. In the second case, however, the onset of embolism before the commencement of labour was unusual and appeared to contradict some of the generally accepted ideas regarding the aetiology of this condition.

Mallory *et al.* (1950) state that the condition usually occurs in the presence of a large foetus and strong uterine contractions. It is generally held that the escape of amniotic fluid through the vagina is prevented by the head engaging the pelvis and the fluid is forced into the uterine veins by the strongly contracting uterus. In this instance not only was the head not engaged in the pelvis but uterine contractions were not established.

It is of interest that rupture of the membranes was not observed to occur in either case,

although clear evidence of rupture was found at autopsy. In both instances liquor may well have escaped during micturition; the frequency complained of by the second patient may well have been due to the escape of liquor. Bowden and Abrahams (1950) describe a fatal case of amniotic embolism in which the membranes were not found to be ruptured at autopsy. It is difficult to understand the mechanism of amniotic embolism under such circumstances, unless one postulates a tear in the placenta.

Shotton and Taylor (1949), Wyatt and Goldenberg (1948), and Sluder and Lock (1952) describe the presence of epithelial squames in the arterioles of the systemic circulation, notably in the myocardium, in fatal cases of amniotic embolism. In Shotton and Taylor's case these were possibly due to parodoxical embolism, as a defect in the interauricular septum was present; in the other 2 the material must have passed through the lung capillaries. It was thought that small haemorrhages, seen in the first case in brain, heart and stomach, might have been the result of systemic emboli, but careful search of a number of sections from brain and heart failed to reveal any foreign material in blood vessels.

Weiner and Reid (1950) emphasize the frequency of haemorrhages in amniotic embolism; of 22 examples reviewed by them, 15 had such manifestations. A striking feature of both our autopsies was the absence of blood clot either in the heart or great vessels, a finding also noted by Shotton and Taylor. Instances of amniotic embolism have also been described in which the clotting time of the blood was shown to be greatly prolonged after collapse had occurred (Eames, 1952; Ratnoff and Vosburgh, 1952).

We have been unable to demonstrate any alteration in the coagulation time of the blood when amniotic fluid or amniotic fluid together with meconium have been injected intravenously into rabbits. Schneider (1953) has found an increased blood coagulation time following the intravenous injection of meconium into dogs. This he found to be due to the presence of a heparin-like anti-coagulant which was released into the circulation during shock. A greatly prolonged coagulation time may well be of diagnostic significance in amniotic embolism.

The second case is of importance as diagnosis could only be made by frozen sections of the lung stained to demonstrate fat. As far as we are aware, no similar case has previously been reported.

Summary

(1) Two fatal cases of amniotic embolism occurring in healthy primiparae are described.

(2) In one of these the embolic material was of a fatty nature and the diagnosis could only be made from lung sections stained for fat.

(3) The effect of amniotic embolism on blood coagulation is discussed.

We wish to thank Mr. D. W. Currie under whose care the first case was admitted to hospital. We are indebted to Dr. A. J. Swanton, H.M. Coroner for the City of Leeds, for permission to publish the second case. Mr. J. Hainsworth was responsible for the photography.

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FIG. 1

Case No. 1.—A medium-sized branch of the pulmonary artery containing masses of pink-staining stringy material, epithelial squames and lanugo hairs. The surrounding lung tissue is oedematous and congested. H. & E. ×100.

FIG. 2

Case No. 1.—Pulmonary arterioles blocked by similar material. H. & E. ×250.

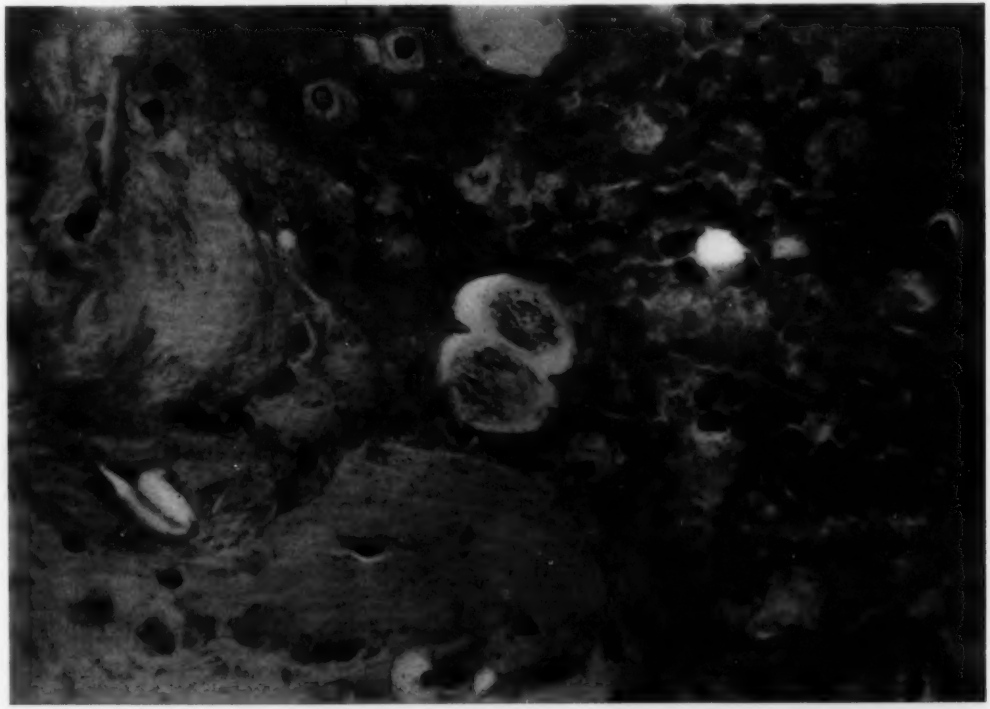

FIG. 3

Case No. 1.—Two lanugo hairs surrounded by blood clot and amniotic debris from the vessel in Fig. 1. H. & E. ×450.

R.G.D., W.G., C.J.P.

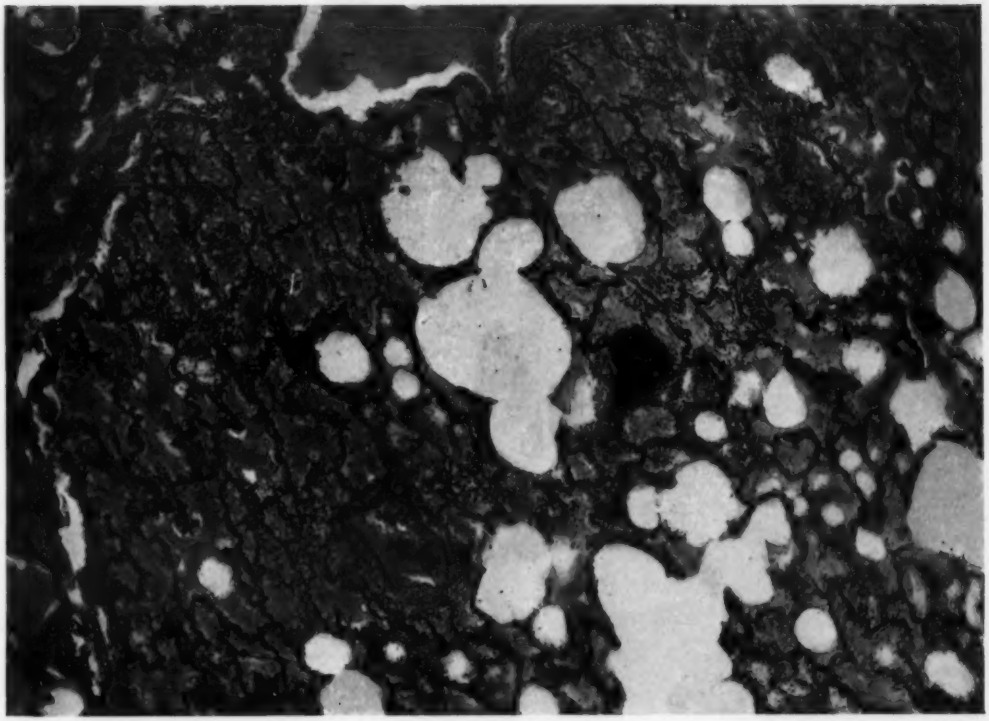

FIG. 4

Case No. 2.—Two small branches of the pulmonary artery containing granular fatty material. Lung alveoli filled with oedema fluid. Scharlach R. ×125.

THE BACTERIOLOGY OF THE PUERPERAL UTERUS

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THE investigations described here are the outcome of our previous work on puerperal pyrexia (Calman and Gibson, 1953). It seemed to us that there were three facets of this subject, each of which was investigated separately. The individual investigations are first described, and then the results of all three are discussed together.

The first investigation consisted of serial high vaginal swabs taken from normal puerperal women; the second of a comparison between high vaginal swabs and samples of uterine contents taken with Little's tubes from apyrexial patients; and the third a similar experiment on a group of pyrexial cases.

In the first investigation we cultured high vaginal swabs taken from normal cases at intervals of 0, 8 and 80 hours after delivery. In 37 cases all three specimens were obtained, in a further 11 cases only the first two swabs were taken and in another 16 cases the first specimen alone was taken. The methods of cultivation were the standard procedures as previously described by us (loc. cit.). Any patient who subsequently developed a temperature was excluded from the investigation.

RESULTS OF SERIAL HIGH VAGINAL SWABS IN NORMAL CASES

The results of this investigation are presented in Table I, which shows the numbers of organisms isolated at the different times after delivery. These have been divided into primary and secondary organisms on a basis of predominant growth. No case was allocated more than one primary organism, and therefore in some instances the division was not well defined. None of the patients having organisms which would normally be regarded as pathogenic had any rise of temperature within 3 days of the swab being taken. The records of these cases were specially examined after the conclusion of the investigation to verify this point. For example, in 3 cases haemolytic streptococci (Groups B and G) were found in the high vaginal swab taken at 8 hours and the patients remained apyrexial. In a further 2 patients *Staphylococcus aureus* was found at 8 hours and neither of these developed a temperature.

The low incidence of anaerobic streptococci isolated is in contrast with the incidence found in the series of pyrexial patients we described in 1953. Examination of Table I shows the expected increase in swabs giving a growth of organisms 80 hours after delivery. The sterile swabs taken 0 and 8 hours after delivery may well represent the result of using antiseptics in the labour ward. Among the 32 cases, the swabs from which gave a growth immediately after delivery, there were 6 which yielded sterile cultures at 8 hours. In 11 out of 37 cases the same organism was isolated from all 3 specimens.

From this preliminary investigation of the normal high vaginal swab it was apparent that most of the common pathogens could be grown from apyrexial patients, and the problem then became to assess their significance in patients with pyrexia, as well as to determine the organisms actually present in the cavity of the uterus. With this object in view, we decided to obtain samples of the actual contents of the uterus for

TABLE I

	0 hours		8 hours		80 hours	
	Primary	Secondary	Primary	Secondary	Primary	Secondary
Sterile	14		14		1	
Staphylococcus cureus	—		2		—	
B. Haemolytic Streptococcus:						
Group B	1	—	2	—	3	—
Group D	1	—	3	1	2	—
Group G	—	—	1	—	—	—
Non-Groupable	1	1	1	—	5	—
Streptococcus viridans	2	—	1	—	2	—
Anaerobic Streptococcus	3	—	—	—	2	1
Non-Haemolytic Streptococcus	3	—	2	—	2	1
B. coli	7	19	2	13	11	16
B. proteus	2	—	2	—	2	1
Staphylococcus albus	21	16	16	10	6	20
Diphtheroids	8	19	2	16	1	15
Monilia	1	6	—	—	—	—
Total	64		48		37	

culture and compare the results with those from high vaginal swabs.

Methods. The high vaginal swabs were cultured by the same methods as before. The samples of lochia from the uterine cavity were obtained by using the modified form of Little's tube described by Stander (1945). This consists (Fig. 1) of a curved glass tube which contains a small piece of rubber lubricated with vaseline, that can be drawn back by means of a piece of thread. After insertion into the uterus the cord is pulled and some of uterine contents drawn into the tube. The tube is then removed and replaced in its sterile container. At the laboratory the tube is flamed and cut with a glass cutting knife about the middle of the column of lochia. A sterile wire is then passed into the lochia at the cut surface and two blood agar plates inoculated; in most cases a Robertson's meat broth was also inoculated. In all instances a direct film was made from the contents of the tube, and this was stained by Gram's method.

Selection of Cases. The cases for whom lochial samples were taken were selected at random throughout the hospital on various days of the puerperium, the only condition being that their temperature had not been raised at any time. The group therefore included patients who had forceps deliveries, episiotomies, tears, etc., as well as normal cases; if, after the sample had been taken, the temperature rose, the case was excluded. Second samples were taken from some cases in order to verify that no infection was introduced by the passage of the Little's tube.

Though the day on which the swab was taken was recorded, it was obviously not easy to differentiate, for example, the late 5th day from early 6th day, and therefore the results have been grouped together for 5th, 6th and 7th days, also 8th, 9th and 10th days, the first 4 days being considered individually.

The febrile cases were selected from those patients in whom the temperature reached the notifiable standard of 100·4° on one occasion; in all cases a catheter specimen of urine was taken and a full clinical examination carried out, in order to exclude other causes of pyrexia. There remained the group of pyrexial patients who, all too frequently, would be classed as genital tract infections, solely because no other obvious cause existed for their temperature and a potentially pathogenic organism had been grown from a high vaginal swab. As we have previously shown, such organisms can, in many instances, be grown from apyrexial patients.

RESULTS OF LOCHIAL SAMPLES IN NORMAL CASES

The general results of this part of the investigation consisted of the bacteriological findings

on the high vaginal swabs and the lochial samples taken from 120 normal afebrile patients.

In the majority of instances the cultures yielded a variety of different organisms, for example, a mixed growth of *Staphylococcus albus*, *Bacterium coli* and diphtheroids, the relative importance of which was difficult to assess. We have therefore shown such cultures as mixed flora and have made no endeavour to report the individual organisms. Where, however, organisms which are commonly regarded as pathogenic, such as *Staph. aureus* and haemolytic streptococci, were isolated, the presence of these has been recorded, though, in fact, they were part of a mixed growth. We have carefully considered adopting the system used by Stander and others, in which every organism isolated is recorded individually. Many samples will produce a growth of several different organisms, and therefore the total number of organisms isolated will greatly exceed the number of specimens taken. We feel that this gives disproportionate weight to organisms such as *Staph. albus*, which are generally thought to be of no significance, and therefore in the interests of producing a clear and compact table we have found it convenient to use the group entitled "mixed flora".

Table II shows the numbers of high vaginal swabs and lochial samples giving a growth on primary culture on blood agar. It will be seen that no sterile high vaginal swabs were obtained, that the number of sterile lochial samples decreased as the puerperium advanced and that taken over all about half the patients had sterile lochial samples on primary culture on blood agar. When, however, the same samples were inoculated into Robertson's meat broth, there was often a scanty growth, though, as explained below, we think that the results obtained on blood agar more accurately reflect the bacterial population of the uterine contents. In the direct smear made from lochial samples organisms were rarely seen, and in no cases were intracellular organisms found. In general, those samples that showed no organisms in the film were those which were sterile on direct plating. The significance of these findings will be discussed further in connexion with the pyrexial cases.

Table III shows the organisms isolated from the high vaginal swabs and lochial samples taken during the first 10 days of the puerperium. We felt that any attempt to divide these organisms according to the day of the puerperium would necessitate working with such small numbers as to make their evaluation unsatisfactory. We have

TABLE II

Plate culture results of H.V.S. and lochial samples from 120 normal cases

Day	H.V.S.		Lochial Samples	
	Growth	No Growth	Growth	No Growth
			Per cent	
1st ..	9	—	3 (33)	6
2nd ..	20	—	7 (35)	13
3rd ..	31	—	17 (55)	14
4th ..	15	—	10 (66)	5
5th, 6th, 7th ..	29	—	17 (58)	12
8th, 9th, 10th ..	16	—	9 (56)	7
	120	0	63	57

TABLE III

Normal Cases

	H.V.S.	Lochial Samples
Mixed Flora	80	37
Mixed Flora from Robertson's only	—	21
Sterile	—	36
Staphylococcus aureus	3	1
B. Haemolytic Streptococcus:		
Group A	—	—
Group B	1	—
Group C	4	2
Group D	13	7
Group G	1	1
Non-Groupable	8	5
Streptococcus viridans	1	—
Anaerobic Streptococcus	—	—
Non-Haemolytic Streptococcus ..	1	3
B. coli (alone)	2	2
B. proteus	4	3
Cl. welchii	1	1
Fusiform	1	1
	120	120

therefore simply recorded totals for high vaginal swabs and lochial samples respectively.

Results of Pyrexial Cases

The results on the pyrexial cases have been recorded in Tables IV and V. These tables have been compiled in a similar manner to Tables II and III, and are directly comparable. The striking feature of Table V is the presence of a number of cases of Group A streptococcal infection. With the majority of these cases the organism was isolated from both the high vaginal swab and lochial sample. From the lochial samples the direct films showed many pus cells and organisms, and in four of the cases the organisms were intracellular as well as extracellular (shown in Fig. 2). In contrast with the apyrexial cases organisms were frequently found in both high vaginal swab and lochial sample in the earlier days of the puerperium. The number of lochial samples showing sterile culture was fewer than in the afebrile cases, and, of course, the high vaginal swabs all produced a growth. In no instance was a pathogen isolated from the lochial sample which was not found in the high vaginal swab. In one instance a Group A streptococcus was found in the high vaginal swab, and not in the lochial sample. This patient was investigated as a contact of an established case, and presumably the organism had not spread to the uterus at the time of taking the lochial sample. It is interesting that we isolated anaerobic streptococci from 3 lochial samples, and that the direct film showed gram-positive cocci. This would suggest that the organism was invading the uterine cavity and was not merely a saprophyte in the vagina.

Of the 2 cases in which a non-haemolytic streptococcus was found in the high vaginal swab, one showed a very poor growth of a non-haemolytic streptococcus from the Robertson's broth inoculated with uterine contents. The other showed no growth of non-haemolytic streptococci, but a mixed flora with coliform predominating, and, on the whole, it was doubtful if this organism was pathogenic in these cases. The same difficulty appeared with the non-groupable streptococcus (not Lancefield A, B, C, D or G) though in one instance this organism was isolated in mixed culture from the high vaginal swab and in pure culture from the lochial sample. In this case the possible pathogenic rôle of the organism appeared stronger than in the other two.

In only one case was a fusiform organism isolated, despite careful attempts to secure the organism from all material. While we are unable to confirm reports isolating this delicate organ-

Table IV

Plate culture results of H.V.S. and lochial samples from 43 pyrexial cases

Day	H.V.S.		Lochial Samples	
	Growth	No Growth	Growth	No Growth
			Per cent	
1st ..	—	—	—	—
2nd ..	5	—	4 (80)	1
3rd ..	12	—	12	—
4th ..	6	—	5 (83)	1
5th ..	5	—	2 (40)	3
6th ..	2	—	2	—
7th ..	3	—	1 (33)	2
8th ..	3	—	1 (33)	2
9th ..	1	—	1	—
10th ..	6	—	6	—
	43	0	34	9

Table V

Pyrexial Cases

	H.V.S.	Lochial Samples
Mixed Flora	20	19
Sterile	—	7
Staphylococcus aureus	1	—
B. Haemolytic Streptococcus:		
Group A	7	6
Group B	1	1
Group C	—	—
Group D	1	1
Group G	—	—
Non-Groupable	3	2
Streptococcus viridans	—	—
Anaerobic Streptococcus	3	2
Non-Haemolytic Streptococcus ..	2	1
B. coli (alone)	1	1
B. proteus	3	2
Cl. welchii	—	—
Fusiform	1	1
	43	43

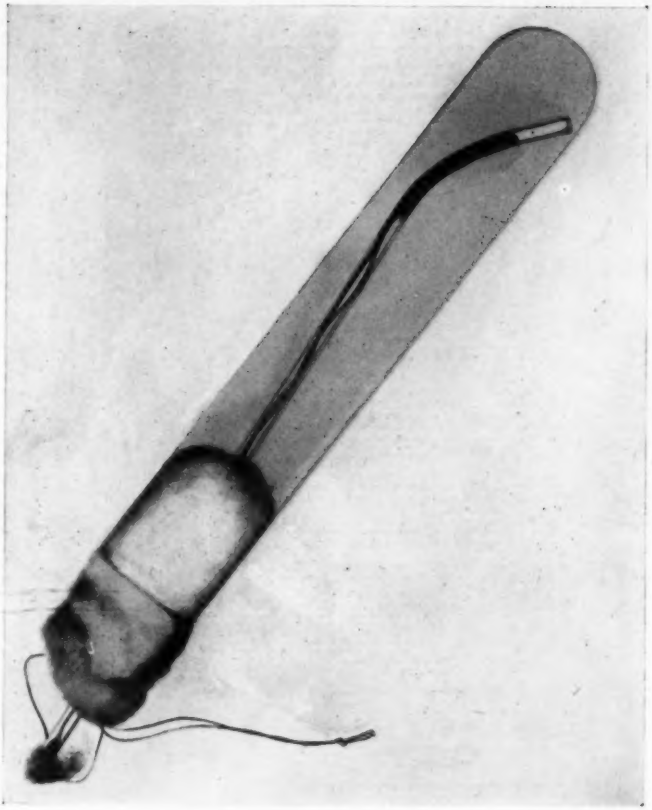

FIG. 1

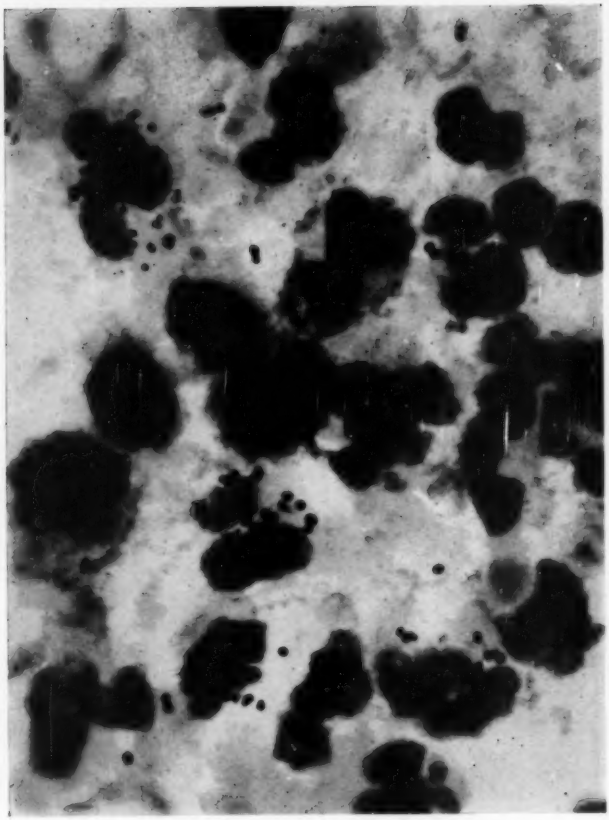

FIG. 2

R.M.C., J.G.

ism from a high percentage of vaginal swabs, we feel that its possible significance as a pathogen in puerperal infection must be further investigated.

Clinical Findings

During the period covered by all our investigations there were two small groups of patients in whom clinical observation suggested the nature of the bacteriological findings, in all other cases there seemed to be little or no correlation. One group consisted of those patients with a persistent low grade pyrexia and no localizing physical signs, and these were sometimes associated with the finding of anaerobic streptococci in the lochial sample. The other and more important group contained some of the patients affected by the Group A haemolytic streptococcus. In only 3 of the 14 cases reported by Gibson and Calman (1953) were the physical signs so marked and the general picture so typical that one could be confident of the bacteriology confirming the clinical diagnosis. In the remaining 11 patients the physical signs were equivocal, probably because they were seen early in their disease. It was in such cases that examination of the direct smear made from the lochia was so helpful, for, while it is true that the organisms were frequently grown from the high vaginal swab within 18 hours, the method of taking lochial samples often gave a significant and helpful result within a few minutes.

Many of these cases could, of course, have been treated empirically with similar results, but we have always opposed this principle, in view of the tendency of organisms to develop resistance to antibiotics. Furthermore, cases exactly similar on clinical grounds are not found to have any significant organisms and would therefore be treated unnecessarily.

Conclusions

It appears to us that the lochial sample cultured on solid media and examined by direct examination of gram-stained film gives a clearer picture of the bacteriology of the puerperal uterus than is obtained from the use of a high vaginal swab.

There is no doubt that where the pathogen is the Group A streptococcus the high vaginal swab will give as accurate a result as the lochial sample, though perhaps not so rapidly. This does not involve use of the technique described by Butler (1946), who also examines fresh smears, but seeks to determine pathogenicity on a basis of capsule formation. The lochial sample does, however, eliminate a great many cases in which the high vaginal swab produces a mixed flora of doubtful significance.

Culture of the uterine contents obtained by a Little's tube, in a fluid media such as Robertson's, tends to give a picture indistinguishable from a high vaginal swab. We are not convinced that, in fact, this represents organisms which are actually invading the uterus, but that the small number of bacteria necessary to produce a growth in these rich media can be accounted for by the passage of the Little's tube and other stray organisms reaching the uterus. When, however, a good growth was obtained from the lochial sample on solid media, it was apparent from the direct examination that the organisms were present in large numbers and this could only occur if they were actively growing in the uterine lumen. The differences obtained by these varying methods of culture serve to emphasize the difficulties in comparing results obtained from different hospitals, since techniques vary considerably. It is, of course, no longer necessary to emphasize the essential anaerobic plate, but even the time for which this is incubated will seriously influence the results obtained.

While we cannot pretend that the routine use of lochial samples would explain all the disputed cases of puerperal pyrexia, we nevertheless consider that it can contribute something towards accurate diagnosis and rational treatment.

We are grateful to Dr. J. Murray for helpful suggestions throughout, and to the members of the consulting staff of the hospital for access to the cases.

We are also glad to acknowledge the assistance of Dr. A. J. Cashman with the bacteriology during the period of this investigation.

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OVARIAN SURVIVAL FOLLOWING HYSTERECTOMY*

BY

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INTRODUCTION

THE object of this paper is to present the results of an investigation carried out to determine the length of survival and mode of function of the ovaries following hysterectomy. The work was prompted by the disagreement between gynaecologists over the management of the younger patient requiring hysterectomy. Most gynaecologists seem to hold the view that in younger women ovarian tissue should be preserved if at all possible, probably even up to the age of 45. They adopt this attitude in the belief that the ovaries continue to function after the uterus has been removed, and that the removal of the ovaries in younger women is liable to precipitate sudden and severe menopausal symptoms. There are others, however, who believe that, if the ovaries are left behind after the uterus has been removed, they only continue to function for a short time. From personal experience of 33 cases Hendry (1936) advised concomitant ovarian removal for the following reasons:

1. The tendency to malignant ovarian change, perhaps accelerated by hysterectomy.

2. The tendency to ovarian cyst formation following hysterectomy.

Hendry did not indicate the age beyond which he favoured ovarian removal, but Crossen (1947) believes that over the age of 43 years the removal of the ovaries with the uterus is an important measure in the prophylaxis of cancer.

Such animal experiments as have been carried out lend weight to the view that the ovaries continue to function after the uterus has been removed. Burford and Diddle (1936) found no ovarian alterations in monkeys 7 months after hysterectomy, and Van Wagenen and Catchpole (1941) demonstrated that hysterectomy did not delay the re-establishment of ovarian function in post-partum monkeys. It seems probable that the chance of ovarian survival after hysterectomy depends upon an adequate vascular and nervous supply to the ovary; Keitler (1904) showed that in the rabbit, where the ovarian blood supply is independent of the uterine arteries, ovarian atrophy does not occur after hysterectomy. In the view of Hoffman (1944) the effects of hysterectomy are variable. In cases in which post-operative ovarian failure has occurred, it is difficult to decide whether it is due directly to the effect of uterine removal, or to nervous and vascular damage to the ovary at the time of operation (Richards, 1951). Krane (1939) was able to demonstrate a cyclical rise and fall in oestrogen secretion as late as 6 years after hysterectomy.

The investigation of ovarian function to be described was carried out by means of vaginal smears taken at frequent intervals, and in many cases daily. The use of vaginal smears was considered to be a more informative means of assessing ovarian function or failure than the recording of hot flushes (Richards, 1951).

HISTORY

Morau (1889), Lataste (1892) and de Retterer (1892) were the first workers to observe that the vaginal epithelium of rodents altered at the time of oestrus and ovulation. Stockard and Papanicolaou (1917) and Long and Evans (1922) reported their observations on the vaginal cytology of guinea-pigs and rats respectively. They all employed a similar technique, and were able to demonstrate the changes that the vaginal epithelium underwent at ovulation and oestrus. They also showed that these

* This work was largely carried out during the tenure of a grant from the Research Grants Committee of the Middlesex Hospital

changes were reflected by cells shed from the vaginal epithelium and examined as a smear. In 1943 de Allende, Shorr and Hartman published their paper on the vaginal cytology of rats. In this work they were able to confirm by laparotomy that changes in the vaginal smears mirrored the changes which occurred in the ovaries. Papanicolaou published conclusions on human vaginal cytology as early as 1933, and since then observations on humans have been made by many observers, notably Papanicolaou, Traut and Marchetti (1948), and de Allende and Orias (1950). The conclusion appears inescapable that during the reproductive life of woman the vaginal epithelium undergoes rhythmical changes, mirroring the changes that occur in the ovary, and that these changes in the epithelium are accurately reflected in changes of cell type, form and distribution as seen in vaginal smears. Rubenstein and Duncan (1941) demonstrated that there was a close correlation between the pattern of the vaginal smear and the level of urinary oestrogen excretion, and they considered that the vaginal smear was a reliable qualitative and quantitative test for the presence of oestrogens. It should therefore be possible to diagnose the presence or absence of oestrogen secretion by the examination of suitable vaginal smears, and under favourable conditions to state whether or not ovulation has taken place. As will be shown later, however, it is usually a matter of considerable difficulty to detect ovulation, and in a small series of cases personally investigated there did not seem to be a close correlation between the appearance of the vaginal smear and the luteal phase as displayed in the uterine endometrium by biopsy. There are some authorities who doubt the value of vaginal smears either as a means of diagnosing ovulation or of assessing the excretion of progesterone. Both Hoffman (1944) and Neustaedter and Mackenzie (1944) believe that endometrial biopsies are of greater value in the diagnosis of ovulation. McLaren (1941) doubted the accuracy of vaginal smears in reflecting ovarian function or even the histology of the vaginal epithelium. Venning and Browne (1937), however, considered that the vaginal smear was as accurate a method as the estimation of pregnanediol excretion for the diagnosis of ovulation.

It was because of this doubt of the value of vaginal smears that it was considered necessary, before investigating women who had undergone hysterectomy, to attempt to correlate vaginal smears with vaginal and endometrial biopsies. This was done by taking vaginal smears from patients in hospital before either an abdominal hysterectomy or repair of prolapse. In the cases of repair of prolapse an endometrial biopsy was obtained by curettage at the time of the operation.

Technique

As the technique used to obtain, stain, examine and correlate vaginal smears was the same throughout both the preliminary and main experiments, it will now be described in detail.

Under direct vision, using a bivalve speculum, a curved glass pipette was introduced high into the posterior fornix of the vagina, and secretion was aspirated into the pipette. (It is important not to aspirate material from the lower one-third of the vagina. Cells shed from this area are difficult to interpret and the findings are often misleading, partly because of external influence acting upon the lower part of the vagina, and partly because of its different embryological origin.) The material thus aspirated into the pipette is projected on to a clean glass slide. Light teasing out of mucoid material is permissible, but firm handling may result in the breaking up of cell agglutinations which are of importance in subsequent interpretation. The smear thus made is immediately placed in a bath of fixing solution composed of equal parts of ether and 95 per cent alcohol. It is most important not to allow the smear to dry. The smear may be safely kept in the fixing solution for periods of up to 1 month. It should be remembered, however, that this solution is highly volatile. A less volatile and equally satisfactory fixing solution is composed of 7 parts of terbutyl alcohol and 3 parts of industrial spirit. It is worth noting here that a smear taken during menstruation can be made relatively easy to interpret by washing it in 1 per cent acetic acid. Any smear taken during menstruation may, apart from vaginal cells, contain cells from the endocervix or endometrium.

The actual mode of staining used throughout these experiments closely follows that described by Shorr (1941). The slides are removed from the fixing fluid, washed in 95 per cent alcohol and twice in distilled water. They are then stained with Shorr's trichrome stain for about 90 seconds:

Ethyl alcohol (50 per cent) ..	100 ml.
Biebrich scarlet (water soluble)	0·5 g.
Orange G.	0·25 g.
Fast green F.C.F.	0·75 g.
Phosphotungstic acid, C.P. ..	0·5 g.
Phosphomolybdic acid, C.P. ..	0·5 g.
Glacial acetic acid	1·0 ml.

The stain is then washed off in two rinsings of distilled water, and 95 per cent alcohol is applied. The smear is then immersed in absolute alcohol for 5 minutes, and transferred to a xylol bath. After clearing it is mounted in Canada balsam.

This somewhat modified Shorr technique was found to be quick and simple to carry out, and gave excellent cytoplasmic definition. A modified Masson trichrome stain as described by Foot (1938) was tried and found to be no more reliable than the far simpler technique described above. Mack (1942) described a method involving the suspension of the smear over a solution of iodine. The method is simple but the smear unfortunately does not constitute a permanent record, as fading occurs in 24 or 48 hours.

After mounting, the smear is examined under the microscope. Three predominant cell types are seen in smears from patients under different conditions and of different ages. Before puberty most of the cells seen are round, stain blue and have relatively large nuclei. These are the basal cells, and come from the deeper, non-cornified layers of the epithelium. During reproductive life, the cells seen in the smear are considerably larger than the basal cells, have smaller nuclei, and are polygonal in shape. Some of them stain blue whilst others stain pink or red. The blue-staining cells come predominantly from the intermediate layers of the vaginal epithelium, and the pink or red staining cells are from the superficial or cornified layers of the epithelium, and their colour is due to the staining of the eleidin contained in the cells (Fig. 1). During reproductive life there is, in the normal case, a rhythmic variation in the number of cornified cells present in the smear. The number is greatest at the mid cycle, and is almost certainly related to ovulation. This rhythm can be well illustrated by plotting the percentage of cornified cells present against time (Fig. 2). (The left-hand side of this figure also indicates the high percentage of basal cells present in the vaginal smear before puberty.) After the menopause and when ovarian atrophy occurs, basal cells appear in large numbers (Fig. 3).

The results of the preliminary experiment described previously are shown in Table I. The number of cases dealt with is small, but it shows that there is a close correlation between the vaginal smear and the vaginal endometrial biopsies, both during reproductive life and after the menopause. (An *active* vaginal smear is one in which cornified cells are present and basal cells absent; an *atrophic* smear contains basal cells; an *active* endometrial biopsy shows evidence of ovarian function, whereas an *atrophic* endometrium fails to reflect any evidence of ovarian activity; a *cornified* vaginal biopsy shows the three layers previously mentioned and there is evidence of superficial cornification which is absent in the thinner

TABLE I

Analysis of 37 Cases undergoing Repair of Prolapse, and 23 Cases undergoing Abdominal Hysterectomy

Operation	Vaginal Smear		Endometrial Biopsy		Vaginal Biopsy	
	Active	Atrophic	Active	Atrophic	Cornified	Atrophic
Repair of Prolapse, 37 Cases						
Pre-menopausal, 19 Cases ..	19	0	19	0	19	0
Post-menopausal, 18 Cases ..	3	15	0	9*	2	16
Abdominal Hysterectomy, 23 Cases	22	1	23	0	—	—

* Not all cases of post-menopausal prolapse had a curettage performed; a few had had a previous hysterectomy.

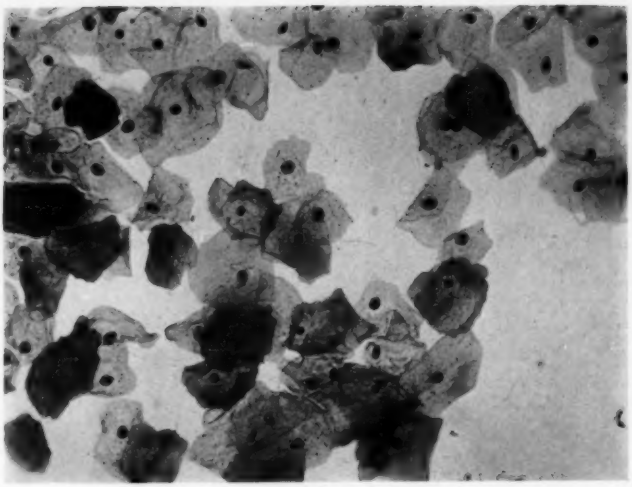

FIG. 1

Smear from patient during reproductive life, showing cornified and intermediate cells. The cornified cells appear somewhat darker than the intermediate ones. (Day 13 of 27 day cycle.)

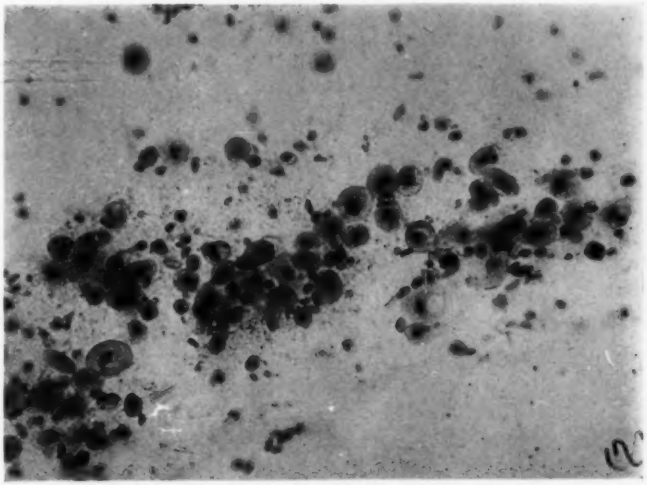

FIG. 3

Smear from post-menopausal patient. Basal cells and leucocytes only present. Much mucus present.

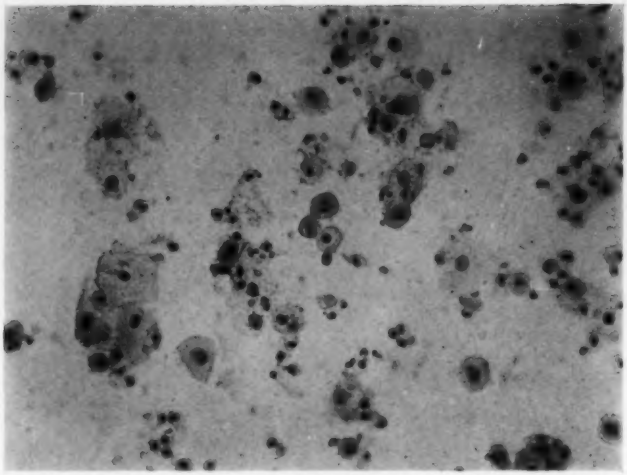

FIG. 4a

Atrophic smear from post-menopausal patient showing many basal cells and some intermediate ones. Leucocytes present in large numbers.

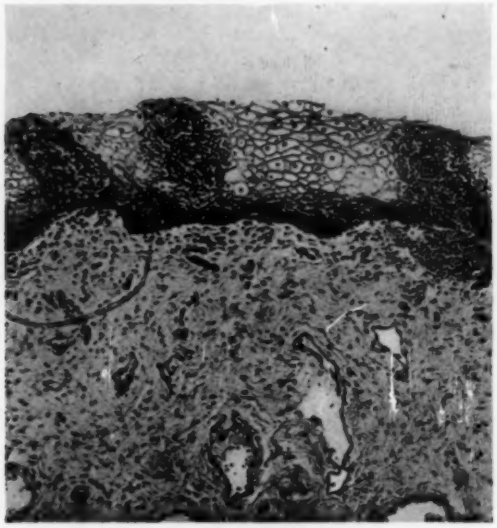

FIG. 4b

Vaginal biopsy from same case as Fig. 4a, showing thinned epithelium and small haemorrhages in epithelium.

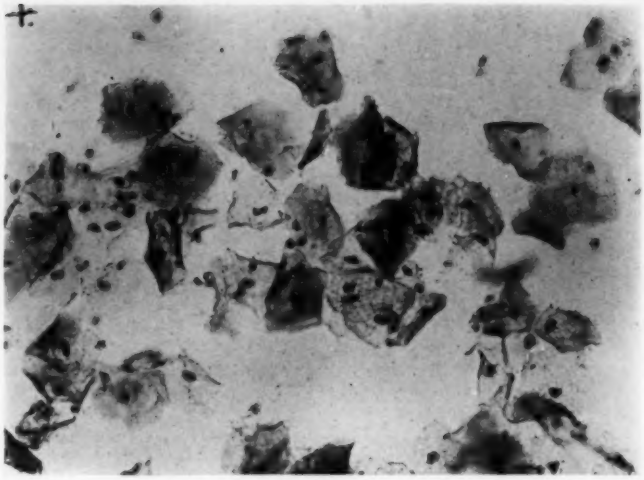

FIG. 5a

Smear from 18th day of cycle showing many cornified cells with some clumping and folding.

FIG. 5b

Vaginal biopsy from same case as Fig. 5a. Note thick cornified epithelium.

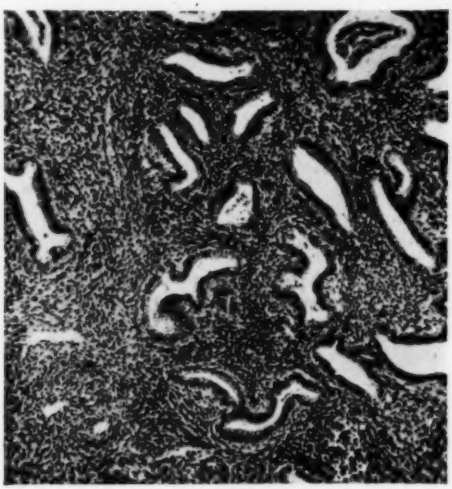

FIG. 5c

Endometrial biopsy from same case as Fig. 5a, showing early secretory changes.

atrophic biopsy. Figs. 4 and 5.) Before a classification of the vaginal smears was made, a total of 300 cells was counted, and, in women with ovarian atrophy, the smears were placed in one of three groups, according to the percentage of basal cells present (de Allende and Orias, 1950):

(*a*) Mild atrophy. Up to 15 per cent of basal cells.
(*b*) Moderate atrophy. 15–40 per cent basal cells.
(*c*) Severe atrophy. More than 40 per cent basal cells.

From the experimental work described above and from the views of other workers, there is ample justification for the view that vaginal smears accurately mirror both the histology of the epithelium and the functional state of the ovaries.

Experiment

The investigation of a series of cases which had undergone abdominal hysterectomy with conservation of ovarian tissue will now be described. The method used to detect residual ovarian function was the examination of serial vaginal smears taken at 2- or 3-day intervals either by the trained nurse or by the patient herself after suitable instruction. The patients had all been operated upon at least 2 years before, and the series was unselected. Patients who had had a hysterectomy performed between the years 1938 and 1950 were contacted by post, and 589 expressed themselves willing to be

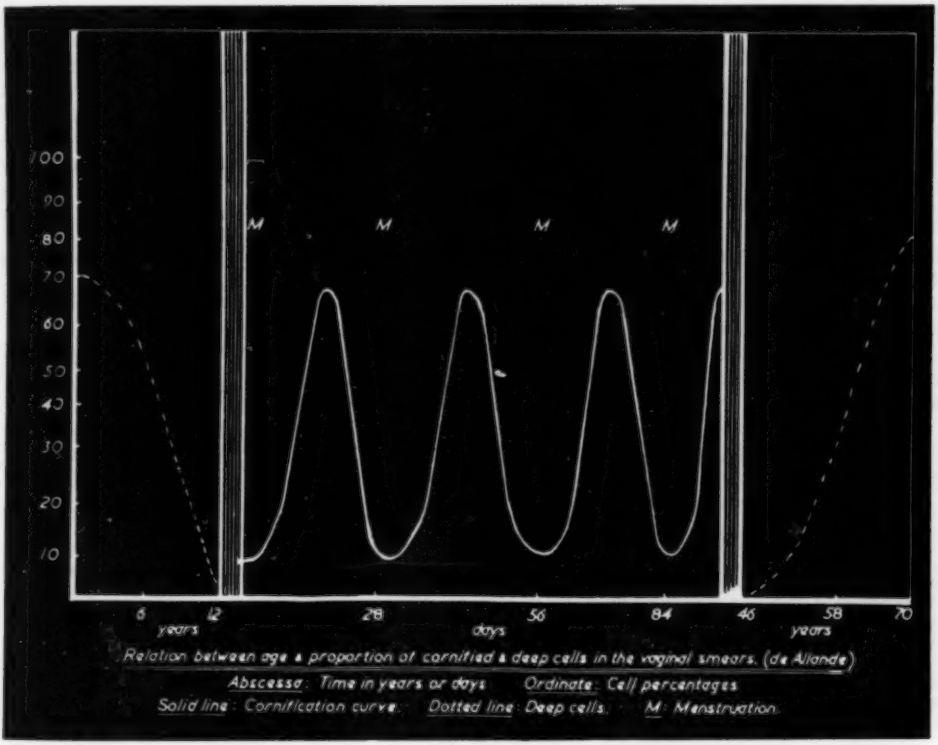

Fig. 2
Relation between age and proportion of cornified and deep cells in vaginal smears. (de Allende.)

examined. All the patients were personally interviewed before serial vaginal smears were embarked upon. The series was constituted as follows:

(*a*) Subtotal hysterectomy	379 cases.
(*b*) Total hysterectomy	210 cases.
Total	589 cases.

Part of the ovarian tissue had also been removed in 67 of the cases of subtotal hysterectomy (Table II), and in 33 of the cases of total hysterectomy (Table III). Because of the small numbers involved, neither of these groups was separated from the main series of subtotal and total hysterectomies. Twenty-one of the total of 589 cases were eliminated because of doubt about the ovarian state at the time of operation, leaving 568 cases for investigation, which for ease of consideration have been considered as one large series.

TABLE II

Subtotal Hysterectomy Combined with Other Pelvic Surgery

Procedure	No. of Cases
With unilateral salpingo-oöphorectomy ..	32
With unilateral oöphorectomy	16
With ovarian cystectomy	13
With unilateral oöphorectomy and ovarian cystectomy	3
With bilateral salpingectomy and unilateral oöphorectomy	3
Total	67

In the great majority of these cases hysterectomy was performed either for fibroids or for menorrhagia associated with various other pathological conditions; 2 cases of carcinoma of the body of the uterus and 1 of sarcoma appear in the series. It is interesting to note that amongst the relatively large number of 379 patients who had undergone subtotal hysterectomy, 39 (11 per cent) unhealthy cervices were found, and 15 of these 39 women denied ever having been pregnant. Twenty-two of them were symptom free, and the remaining 17 complained of either vaginal discharge or post-coital bleeding. No case of carcinoma was detected amongst those cervices subsequently removed surgically.

TABLE III

Total Hysterectomy Combined with Other Pelvic Surgery

Procedure	No. of Cases
With unilateral salpingo-oöphorectomy ..	20
With unilateral oöphorectomy	6
With ovarian cystectomy	3
With unilateral salpingectomy and ovarian cystectomy	2
With unilateral salpingectomy	1
With bilateral salpingectomy and unilateral oöphorectomy	1
Total	33

The investigation of each patient by serial vaginal smears continued for a minimum of 6 weeks, and for the purposes of description the series is divided into (1) those who had their operation performed before the age of 45, and (2) those who had the operation performed after the age of 45. The dividing age of 45 years was chosen as it appears to be widely believed that below this age more vigorous attempts should be made to preserve healthy ovarian tissue than after it, as the symptoms of the surgically induced menopause are more severe in the younger woman. The risk of cancer in the older woman probably also prejudices the gynaecologist in favour of ovarian removal. Table IV

TABLE IV

Hysterectomy performed under the age of 45 years
Total number of Cases, 353

	"Active" vaginal smear		"Inactive" vaginal smear	
	Flushes		Flushes	
	Present	Absent	Present	Absent
Less than 3 years since operation	5	72	2	2
81 cases	77 (95 per cent)		4 (5 per cent)	
Between 3 and 5 years since operation	10	63	10	3
86 cases	73 (85 per cent)		13 (15 per cent)	
More than 5 years since operation ..	34	77	53	22
186 cases	111 (60 per cent)		75 (40 per cent)	

provides an analysis of 353 cases operated upon under the age of 45. The cases are divided into three groups:

(1) Those operated upon between 2 and 3 years ago.
(2) Those operated upon between 3 and 5 years ago.
(3) Those operated upon more than 5 years ago.

(In this Table, as elsewhere in this paper, the term *active* vaginal smear means a smear displaying some degree of cornification; an *inactive* or atrophic smear is one in which cornified cells are almost totally absent and basal cells are present in varying numbers, as described previously.)

Table IV shows that, within 3 years of operation, only 5 per cent of these younger patients had *inactive* (atrophic) smears diagnostic of ovarian failure. This figure had risen to 40 per cent when more than 5 years had elapsed since operation. Table IV also shows that the presence or absence of hot flushes bears little relation to ovarian survival as reflected in the vaginal smear; a considerable number of women with *active* smears suffered from flushes, and an almost equal number with *inactive* (atrophic) smears had no flushes at all. These observations lend weight to the view that the menopausal patient is an unstable and inaccurate observer whose response level to oestrogens is subject to sudden alteration (*Lancet* Annotation, 1953). A much smaller group of women, who had had a minor gynaecological operation performed (endometrial biopsy or curettage, or cauterization of the cervix) under the age of 45 years, was examined and analyzed in the way described in Table IV. The results are presented in Table V.

TABLE V

Curettage or Cautery Performed under the Age of 45 Years
Total number of Cases, 95

	"Active" vaginal smear	"Inactive" vaginal smear
Less than 3 years since operation	27	3
30 cases	(90 per cent)	(10 per cent)
Between 3 and 5 years since operation ..	24	6
30 cases	(80 per cent)	(20 per cent)
More than 5 years since operation	23	12
35 cases	(66 per cent)	(33 per cent)

These patients may be looked upon as essentially normal controls, and it will be noticed that ovarian function in these women as reflected in vaginal smears is very similar to those upon whom a hysterectomy has been performed.

Table VI shows further analysis of those women who had a hysterectomy under the age of 45 years, and who had *active* vaginal smears. The 261 cases were again divided into the same 3 groups in relation to the time since operation, and each of these groups into 3 further subdivisions:

(1) Constant low level of cornification. (Anovular ovarian function with diminished oestrogenic output.)
(2) Fluctuant level of cornification (Fig. 6). (Possible ovulation.)
(3) Persistently high level of cornification (Fig. 7). (Follicular cyst formation in the ovaries.)

There was a reduction from 72 per cent of patients showing a fluctuant level of cornifi-

TABLE VI

"Active" Vaginal Smears in Women upon whom Hysterectomy was Performed under the Age of 45 Years
261 Cases

	Constant Low Level of Cornification	Fluctuant Level of Cornification	Persistently High Level of Cornification
Less than 3 years since operation	15	54	7
76 cases	(20 per cent)	(72 per cent)	(8 per cent)
Between 3 and 5 years since operation	25	46	4
75 cases	(33 per cent)	(61 per cent)	(5 per cent)
More than 5 years since operation	46	45	19
110 cases	(42 per cent)	(41 per cent)	(17 per cent)

cation within 3 years of operation, down to 41 per cent more than 5 years after operation. That the fall in the number of patients showing fluctuant levels of cornification (and therefore possibly ovulating) is probably due to age, rather than to the operation of hysterectomy, is shown in Table VII where a small series of patients attending a clinic for the treatment of vaginal discharge is analyzed. It is seen that with increasing age there is a smaller number showing fluctuant levels of cornification. It must be noted that before these patients could be studied the discharge had to be cured because, apart from the large number of leucocytes which obscure the smear, misleadingly high levels of cornified cells are often obtained. Leucocytes enter the

TABLE VII

63 Cases Ages 25–45 Years Attending a Special Clinic Investigated for Types of Cornification Curves

Age	Number of Cases	Constant Low Level of Cornification	Fluctuant Level of Cornification	Persistently High Level of Cornification
25–38 years	33	4 (12 per cent)	27 (72 per cent)	2 (6 per cent)
38–45 years	30	9 (30 per cent)	13 (43 per cent)	8 (27 per cent)

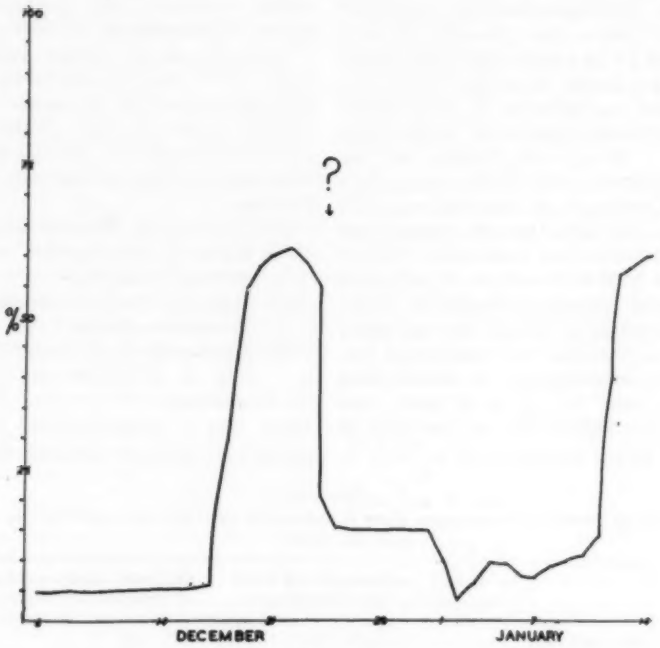

FIG. 6

Cornification curve from patient aged 40. Subtotal hysterectomy and left oöphorectomy performed 3 years previously. Ordinate, percentage of cornified cells; abscissa, time. At point marked with a question-mark the appearances strongly suggested ovulation. (Fluctuant level of cornification.)

vaginal smear by diapedesis, and are therefore also seen under various conditions of thinning of the vaginal epithelium:

(*a*) Before puberty.
(*b*) In castrates.
(*c*) In other cases of ovarian deficiency.
(*d*) After the menopause.

Ninety-two cases with inactive vaginal smears operated upon under the age of 45 years are analyzed in Table VIII. It appears that the number of cases showing the changes of severe atrophy increases with the lapse of years since operation, but the increase is not striking.

Patients operated upon over the age of 45

TABLE VIII

"Inactive" Vaginal Smears in Women Operated upon (Hysterectomy) under the Age of 45 Years
Total number of Cases, 92

	Mild Atrophy	Moderate Atrophy	Severe Atrophy
Less than 3 years since operation .. .. 4 cases	1 (25 per cent)	3 (75 per cent)	0
Between 3 and 5 years since operation .. .. 13 cases	9 (70 per cent)	2 (15 per cent)	2 (15 per cent)
More than 5 years since operation .. .. 75 cases	42 (56 per cent)	16 (21 per cent)	17 (23 per cent)

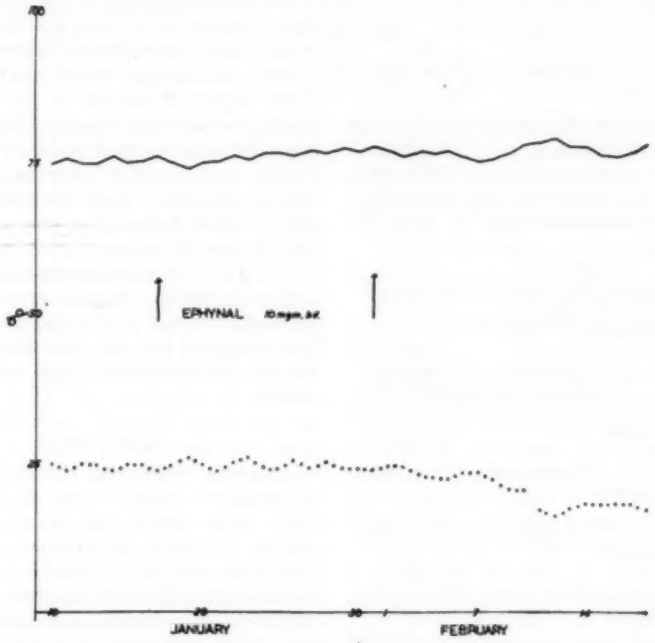

FIG. 7

Curve from patient aged 42. Subtotal hysterectomy performed 10 years previously. Ordinate, cell percentages; abscissa, time.
Continuous line = cornified cells. Broken line = intermediate cells.
(Persistently high level of cornification.)

years are analyzed in Table IX. Two hundred and fifteen cases are presented, and it can be

TABLE IX
Hysterectomy Performed over the age of 45 Years
Total number of Cases, 215

	"Active" vaginal smear		"Inactive" vaginal smear	
	Flushes		Flushes	
	Present	Absent	Present	Absent
Less than 3 years since operation .. 41 cases	8	22	9	2
	30 (75 per cent)		11 (25 per cent)	
Between 3 and 5 years since operation .. .. 51 cases	9	18	18	6
	27 (54 per cent)		24 (46 per cent)	
More than 5 years since operation .. 123 cases	9	18	65	31
	27 (22 per cent)		96 (78 per cent)	

seen that the number of inactive smears rises from 25 per cent within 3 years of operation to 78 per cent after more than 5 years. That this is an expression of age rather than operation seems probable from a study of Table X, where 97

TABLE X
Curettage or Cautery Performed over the Age of 45 Years
Total number of Cases, 97

	"Active" vaginal smear	"Inactive" vaginal smear
Less than 3 years since operation .. .. 32 cases	25 (78 per cent)	7 (22 per cent)
Between 3 and 5 years since operation .. 30 cases	15 (50 per cent)	15 (50 per cent)
More than 5 years since operation .. .. 35 cases	9 (26 per cent)	26 (74 per cent)

patients submitted to minor gynaecological procedures are analyzed for comparison. Three years after operation 22 per cent of these showed inactive smears. This figure had risen to 74 per cent after more than 5 years. A glance at Table IX further emphasizes the misleading evidence of ovarian activity that may be presented by a study of flushing. Salmon and Frank (1936) showed that there was no close correlation between the type of vaginal smear and the presence or severity of flushing. This view was shared by Ottaway (1941) and Bennett and Te Linde (1942).

Table XI shows that, in 84 cases operated upon over the age of 45 and showing active smears, the number displaying a fluctuant level of cornification falls from 29 per cent of those seen within 3 years of operation to 19 per cent if seen more than 5 years after operation. One hundred and thirty-one cases showing inactive smears and operated upon over the age of 45 are presented in Table XII. It may be seen that the percentage of cases of severe atrophy increases from 14 per cent within 3 years of operation to 37 per cent more than 5 years after operation. These findings are in close agreement with those of de Allende and Orias (1950).

Geist and Salmon (1939) found wide variations in the degree of atrophy in the vaginal smear which occurred after the cessation of menstruation, and demonstrated that an occasional case showed persistence of oestrogenic activity for varying periods of time after the cessation of menstruation. It has often been tacitly assumed that the site of origin of such oestrogenic substances produced after the cessation of menstruation must be the ovaries. Several authorities, including Salmon (1939) and Hoffman (1944), have suggested that the adrenals are responsible for the production of these oestrogenic substances.

CONCLUSIONS

It appears, therefore, that the operation of hysterectomy with conservation of ovarian tissue does nothing to hasten the onset of ovarian failure or menopausal symptoms. (It must be remembered, however, that occasionally an *active* vaginal smear may be seen in a patient otherwise undoubtedly post-menopausal.) This statement is true in the case of patients operated upon under the age of 45. Comparison between the results obtained from these cases and a smaller series of normal controls (Table VII) shows a close correlation. In patients operated

TABLE XI

"Active" Vaginal Smears in Women upon whom Hysterectomy was Performed over the Age of 45
Total number of Cases, 84

	Constant Low Level of Cornification	Fluctuant Level of Cornification	Persistently High Level of Cornification
Less than 3 years since operation	17	9	5
31 cases	(55 per cent)	(29 per cent)	(16 per cent)
Between 3 and 5 years since operation	18	8	1
27 cases	(67 per cent)	(30 per cent)	(3 per cent)
More than 5 years since operation	20	5	1
26 cases	(77 per cent)	(19 per cent)	(4 per cent)

TABLE XII

"Inactive" Vaginal Smears in Women upon whom Hysterectomy was Performed over the Age of 45
Total number of Cases, 131

	Mild Atrophy	Moderate Atrophy	Severe Atrophy
Less than 3 years since operation	5	1	1
7 cases	(72 per cent)	(14 per cent)	(14 per cent)
Between 3 and 5 years since operation	14	3	2
19 cases	(74 per cent)	(16 per cent)	10 (per cent)
More than 5 years since operation	32	35	38
105 cases	(30 per cent)	(33 per cent)	(37 per cent)

upon over 45 years of age there is a more marked diminution in the number showing active smears and fluctuant levels of cornification, but again a comparison between these cases and normal patients of the same age-group fails to reveal a more rapid decline of ovarian activity in those patients after hysterectomy.

Analysis of those cases showing active vaginal smears in both age-groups (Tables VI and XI) reveals a fall over the years in the number of cases showing fluctuant levels of cornification (possible ovulation). This fall is seen to be more marked in those cases operated upon over the age of 45 years than in those operated upon under 45 years. It is a well established fact that ovulation becomes less frequent and an anovulatory cycle more frequent as age advances. In the absence of evidence to the contrary it appears likely that this diminution in the number of cases showing fluctuant levels of cornification is of the same order of magnitude as would occur had hysterectomy not been performed.

It appears, therefore, that healthy ovarian tissue should be preserved at all ages, as evidence has been presented that such tissue continues to function for considerable periods of time after hysterectomy; there has in this series been no subsequent development of either ovarian carcinoma or ovarian cysts.

SUMMARY

(1) The technique of obtaining, staining and interpreting vaginal smears is described.

(2) Evidence is presented that vaginal smears reflect ovarian function and vaginal epithelial histology.

(3) Three hundred and fifty-three cases upon whom hysterectomy with conservation of ovarian tissue was performed at least 2 years before were investigated by means of vaginal smears. Less than 3 years after operation 95 per cent showed active vaginal smears. This figure had fallen to 60 per cent more than 5 years after operation.

(4) It is shown that these figures correspond to a control series of 95 cases of similar age-group and similarly investigated.

(5) Two hundred and fifteen patients upon whom hysterectomy was performed over the age of 45 years were similarly investigated, analyzed, and compared with a small group of normal cases. Again it may be seen that there is no significant difference between these two groups.

(6) It is concluded that, following hysterectomy at whatever age, preserved ovarian tissue continues to function for considerable periods of time. Ovarian tissue should, therefore, be spared whenever possible. There is no evidence of subsequent malignant change or cyst formation in such retained ovarian tissue.

I wish to express my thanks to the Research Grants Committee of the Middlesex Hospital for making this work possible. I should also like to thank the various members of the hospital consultant staff who allowed me to examine their patients and also provided much encouragement; the Records Officer, Mr. T. E. Cowan and his staff, for much of the routine follow-up work and also for help with the Tables; also Mr. Turney and Mr. Runicles of the Departments of Photography and Anatomy for their generous help with the illustrations.

I have also to thank Professor C. H. G. Macafee for much help and encouragement.

Figure 2 is reproduced by kind permission of Dr. Inés de Allende from *Cytology of the human vagina*, published by Paul Hoeber Inc. (Publishers), New York.

Staff-Nurse J. Dickens, S.R.N., helped in ways almost too numerous to mention; to her untiring efforts much of the credit for this work is due.

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ECTOPIC CERVICAL TISSUE IN THE VAGINA

BY

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THE occurrence of ectopic endometrium is all too common but the corresponding occurrence of cervical epithelium in situations apart from the cervix is relatively rare. The following case illustrates this rarity.

CASE REPORT

When first seen, Mrs. I.S., aged 35, was complaining of vaginal discharge and "dropping of the womb", both symptoms being of 7-years duration. The vaginal discharge gave rise to no irritation; it was white in colour, had never been bloodstained and had no relation to menstruation. The patient stated that, although the discharge was heavy most of the time, emotional upset of any kind (and particularly sexual intercourse) greatly augmented it. There was also marked stress incontinence; dysuria was absent but there was both diurnal and nocturnal frequency. Menstruation was normal.

Her general health was only fair for she felt run down and tired. Some weight loss was associated with a poor appetite. Her previous general medical history showed nothing of relevance. She had had 6 normal pregnancies, the last one being a twin pregnancy in 1945. All had ended in normal spontaneous deliveries at home, except in the second where she had had a forceps delivery—the reason for which could not be ascertained.

She was an obese and rather despondent, tired-looking woman. Nothing abnormal was found in the cardio-vascular, respiratory, alimentary or central nervous systems. Vaginal examination revealed a gaping vaginal introitus and a deficient and lax perineum. There was uterine prolapse with a large urethro-cystocoele and rectocoele. The cervix showed chronic cervicitis of mild degree. Extending down the whole length of the anterior vaginal wall, from the base of the vaginal cervix almost to the urethral orifice, and out on to the lateral walls of the vagina was a large area of abnormal tissue which appeared to be chronic ulceration; the posterior vaginal wall was similarly affected. The epithelium was thickened, spongy and erythematous, and many of what seemed to be small orifices were scattered over its surface. A thick glairy white discharge literally poured from this tissue. Neither of these areas came within reach of the vaginal portion of the cervix; thus the only normal vaginal epithelium to be seen lay over the vaginal cervix, around the vaginal orifice and in a strip one inch wide down each lateral wall. The uterus and adnexae were normal.

INVESTIGATIONS

The haemoglobin was 92 per cent (13·6 g. per 100 ml.).

Catheter specimen of urine: There was no sugar, but there was a trace of albumen. Many pus cells and some epithelial cells were present on microscopy. Culture gave an abundant growth of *Bacterium coli.*

The Wassermann and Kahn reactions, and the gonococcal complement fixation test, were all negative.

Examination under anaesthesia showed that the discharge coming from the upper part of the ulcerated area was purulent. Microscopy of the discharge demonstrated numerous pus cells and a few epithelial cells; no *Trichomonas vaginalis* were seen. Uterine curettage produced normal-looking curettings; histological examination later confirmed this. A biopsy of the ulcerated area in the vagina was taken and the pathologist's report stated "chronic ulcerated cervix with no evidence of malignancy".

She was given a prolonged course of treatment

designed to clear up the urinary infection and the infection, presumably secondary, in the abnormal vaginal tissue. The urinary infection cleared up quickly, but the discharge remained stubbornly purulent for several weeks. Eventually, however, after a course of oestrogens and the local application of acriflavine emulsion, examination under anaesthesia revealed a non-purulent, but still heavy, thick, glairy discharge. The histological examination of a further biopsy of the vagina showed the tissue to be fibromuscular in type with an extensive invasion of glandular secreting columnar epithelium.

Thus there appeared to be no doubt that the tissue lying in the vagina was cervical epithelium. It was considered that the optimum treatment in this case would be to perform a pelvic floor repair and in doing so excise as much as possible of the abnormal tissue. Thus at operation an anterior colporrhaphy and colpo-perineorrhaphy was performed; all the abnormal tissue in the anterior vaginal wall was excised but a small area in the posterior fornix could not be included in that tissue excised in the colpo-perineorrhaphy. The cervix was cauterized. Recovery from the operation was satisfactory and the operational site healed well.

The excised tissue was examined histologically. This confirmed that both anterior and posterior vaginal walls were extensively invaded by glandular secreting columnar epithelium which was perfectly regular and showed no evidence of malignancy. The tissue was in fact quite indistinguishable from normal cervical epithelium (Figs. 1 and 2).

At follow-up examinations, it was seen that there was very little ectopic cervical tissue left; the pelvic floor repair had healed well; the cervix was healthy. Her symptoms had been cleared up and there was very little vaginal discharge.

Comment

The ectopic tissue produced the typical cervical discharge. It was interesting to note that the patient stated voluntarily and later reaffirmed to direct questioning that emotional factors played a great part in the activity of this tissue. Domestic worries and the more chronic prolonged emotional upsets resulted in greater production of secretion as well as the more acute stimuli such as a vaginal examination.

In regard to aetiology there is some resemblance between this condition and endometriosis; the theories in respect of endometriosis can be well applied here. Direct spread downwards from the cervix may have been possible—a further extension of the process leading to the formation of a cervical erosion. However, in this case, the ectopic tissue was separated from the normal cervical epithelium by normal vaginal epithelium.

Endometrial tissue may occur in the cervix, vagina and perineum. It has been found in an episiotomy scar, probably as the result of direct implantation during delivery. In this case implantation of cervical epithelium in a breach of the vagina during one of the patient's 6 labours was the most likely cause of its occurrence.

I am indebted to Mr. J. B. Joyce for his permission to publish these notes and for his co-operation, and to Dr. J. S. Faulds for the pathological data.

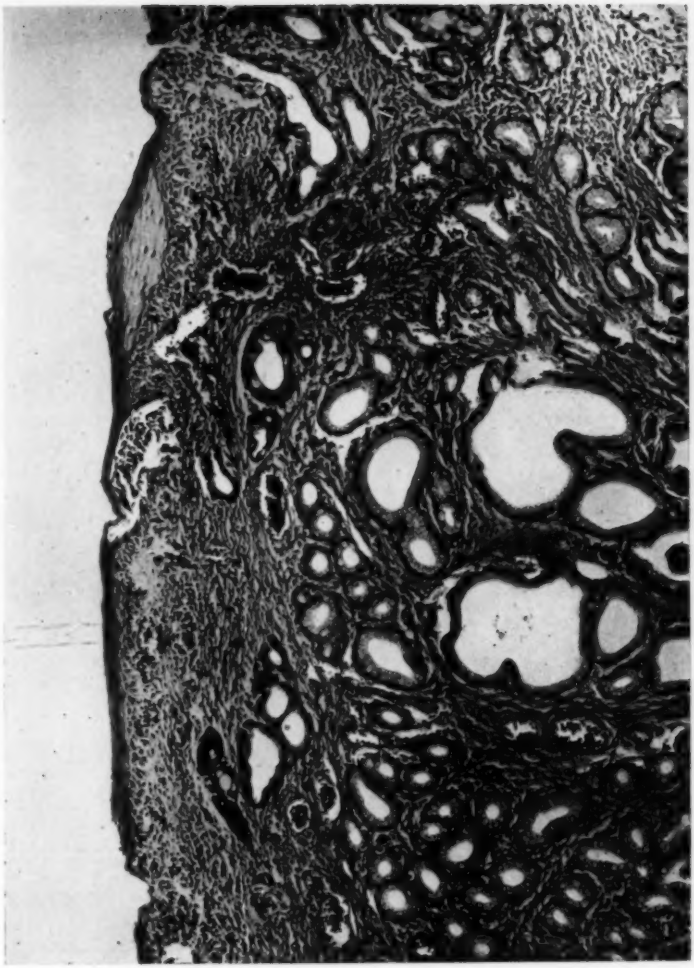

FIG. 1

Section from anterior vaginal wall. ×105.

FIG. 2

Section from posterior vaginal wall. ×105.

THE METABOLISM OF IRON IN PREGNANT PATIENTS TREATED WITH MASSIVE DRIP INFUSIONS

BY

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SINCE it was first observed by Scott and Govan (1951) that iron may be excreted in estimable quantities after intravenous injection of proprietary preparations of the saccharated oxide, several conflicting reports as to the actual amounts lost in the urine have appeared in the literature. Smith (1953) reports that even after massive injections only a very small and negligible percentage of the injected iron is excreted. Crawley (1952) on the other hand found higher levels of excretion. It was, therefore, decided to investigate this problem in cases of pregnancy anaemia, in view of the possible importance of this factor in relation to maternal and foetal iron stores.

Previously, in the treatment of iron deficiency anaemias a system of gradually increasing doses of intravenous iron was employed (Scott and Govan, 1951), but it was found that the amount of iron excreted varied not only with the amount injected but also with the total dosage already given. It seemed advisable therefore to fix these two variables and anaemic patients were given 1 g. of iron by intravenous drip over a period of 8 hours. Serial estimations of the iron content of the urine, faeces and blood were made.

MATERIALS AND METHODS

Six iron-balance experiments were carried out on 6 anaemic patients. All were put on a diet yielding 16 mg. of iron daily. During the fourth day of the diet stools and urine were collected. An intravenous drip of 1 g. of saccharated iron oxide in 2 pints of 5 per cent dextrose was set up on the fifth day and given over a period of 8 hours. Blood (taken from the opposite arm) and urine samples were collected during this period and for some time thereafter. Stools passed in the 24 hours following the setting up of the drip were also collected. The haematological methods were the same as described in previous communications (Govan and Scott, 1949; Scott and Govan, 1951). Iron estimations were made according to the method of Dahl (1948), using potassium thiocyanate to develop the colour, which was read in a photoelectric colorimeter. For the estimation of faecal iron the method of Kennedy (1927) was used.

In order to assess the sensitivity of the method of estimating iron the same technique was applied to solutions of varying strength made up from a freshly prepared stock solution of ferrous ammonium citrate. At high concentrations of iron (600 μg. per cent or more) the error was approximately 1 to 2 per cent. Below this the method was less accurate. At 300 μg. per cent the error had increased to 5 per cent and below 100 μg. per cent it was frequently double this. Apart from the initial readings, however, most of the values obtained in the present experiment lay within the higher and more accurate range.

RESULTS

The first 3 patients were given 1 g. of saccharated ferric oxide (Ferrivenin) intravenously. All were in the last trimester of pregnancy and had microcytic hypochromic anaemias with haemoglobin readings of 8·0 to 8·9 g. per cent and red cell counts over 3,000,000/c.mm. Their initial serum-iron values were nil or very low and no iron was present in their bone marrows which were normoblastic. Prior to the drip no iron was found in the urine and the faecal iron values are shown in Table I. Urine- and serum-

TABLE I

Faecal Iron	Case 1	Case 2	Case 3
	mg.	mg.	mg.
1. Iron content/0·2 g. dried stool	0·087	0·062	0·144
Total iron excreted in 1st 24 hours	7·607	3·86	4·808
2. Iron content/0·2 g. dried stool after drip ..	0·064	0·055	0·324
Total iron excreted in 2nd 24 hours	1·081	4·014	7·752

iron values obtained after setting up the drip are shown in Fig. 1. It will be seen that, during the

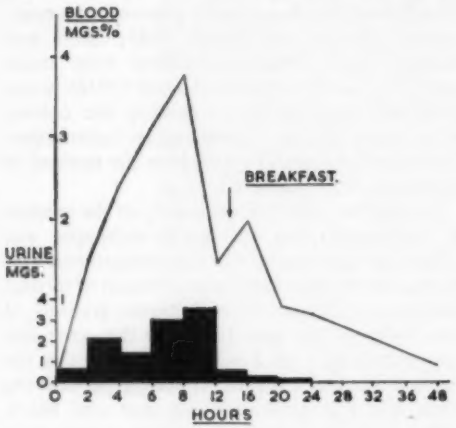

FIG. 1

Average serum- and urine-iron values in 3 patients given 1 g. of ferric iron (Ferrivenin) intravenously.

first 8 hours, while iron was given, both the serum- and urine-iron values mounted rapidly, the serum-iron reaching its peak when the drip was completed. The urine-iron rose even higher in the subsequent 4-hour period. Thereafter the urine values showed a very rapid decline, while the serum-iron fell more slowly and showed a secondary peak, the significance of which will be discussed later. No further excretion of iron was noted in the urine after 28 hours. The average total amount passed was 10·90 mg.

The faecal iron results are shown in Table I. It can be seen that there is no agreement in the figures before and after the drip.

The remaining 3 patients were given 1 g. of saccharated ferrous oxide (Iviron) intravenously. As before all were in the last trimester of pregnancy. Two had haemoglobin values of 8·0 and 8·1 g. per cent respectively. The third patient was much more anaemic. Her haemoglobin was only 5·0 g. per cent. All 3 patients had red cell counts of 3,000,000/c.mm. or more. The serum-iron values were nil or very low. The urine contained no iron. In the two milder anaemias the bone marrow was normoblastic. In the more severe case the marrow was of the normoblastic hypercellular type, with an increased number of early and intermediate erythroblasts. No iron could be seen in any of the marrows. The faecal iron values are shown in Table II.

TABLE II

Faecal Iron	Case 4	Case 5	Case 6
	mg.	mg.	mg.
1. Iron content/0·2 g. dried stool	0·025	0·084	—
Total iron excreted in 1st 24 hours	3·67	3·384	—
2. Iron content/0·2 g. dried stool after drip ..	0·033	0·080	—
Total iron excreted in 2nd 24 hours	0·366	14·850	—

The serum- and urine-iron curves are shown in Fig. 2. The peak value in the serum was reached at 8 hours, when the drip was completed, but this value was less than half that of the Ferrivenin cases (1·59 mg. per cent as compared with 3·75 mg. per cent). The patient with the severe anaemia showed the flattest curve of all. Her peak at 8 hours only reached 0·78 mg. per cent. Though this low figure reduced the average for the group, it did not in any way account for the striking difference between these cases and the Ferrivenin cases, all of whom had peak values over 3·0 mg. per cent.

The urine-iron was also considerably reduced. In the initial stages only small amounts of iron were passed in the urine. Maximal excretion occurred during the last 2 hours of the drip and in the subsequent 4-hour period less iron was passed. Thereafter only traces could be detected, and after 24 hours no further iron was present in the urine. The average amount excreted was

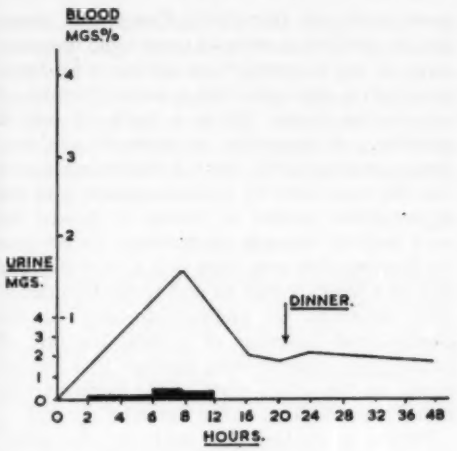

FIG. 2

Average serum- and urine-iron values in 3 patients given 1 g. of ferrous iron (Iviron) intravenously.

1·16 mg. The patient with severe anaemia excreted the least, 1·05 mg.

Faecal iron results are shown in Table II and again there appeared to be no correlation between the administration of iron and the iron passed in the faeces.

Sternal punctures were repeated in these cases 24 hours after commencing the drip and by then iron was demonstrable in the marrows in fairly large quantities.

In the Ferrivenin cases a peculiar secondary rise in the serum-iron levels was noted in the specimens taken after 16 hours. We were at first unable to explain this rise though we felt it might be related to the taking of breakfast some 2 hours previously. In the second group of patients breakfast was therefore omitted and it is interesting to note that the serum-iron continued to fall, but rose again after the next meal.

DISCUSSION

By now it is obvious that anaemic patients do not respond in the same fashion to ferrous and ferric preparations. Both preparations are colloidal solutions of saccharated iron oxide, the only difference being that the former contains bivalent iron and the latter trivalent. Both were given in equal amounts over the same period of time and therefore it seems reasonable to assume that the different valencies of the two preparations were responsible for the resulting variations in serum- and urine-iron levels.

The serum-iron levels showed striking differences. In patients given ferric iron the serum-iron mounted steadily to more than twice the level noted in patients given ferrous iron. Thereafter it fell rapidly but still remained well above that of the second group. At 24 hours the level was still twice as high, but by 48 hours both curves had begun to approximate. The low serum values obtained with ferrous iron suggested that it is being taken up more rapidly by the tissue depots. This is in accordance with the work of Starkenstein and Weden (1928), Vannotti (1946) and Vannotti and Delachaux (1949). These authors showed (in the latter two instances by following radio-active iron) that ferrous salts have a selective effect on the tissues, whereas ferric salts have no biocatalytic activity. They circulate longer and are gradually deposited in the spleen and other depot organs.

One other point should be mentioned. We have already shown that the serum-iron rose in the first 3 cases approximately 2 hours after breakfast. Diurnal variations in serum-iron are known to occur and highest readings are recorded in the morning (Vahlquist, 1949; Hemmeler, 1944). These variations are small and they do not appear to be solely responsible for the marked rise in serum-iron noted above. We felt that the breaking of the fast some 2 hours previously had a greater influence and in the second group of patients breakfast was delayed and the first meal given at lunch time. In this group the serum-iron continued to fall but rose again following the intake of food at lunch time. The rise was not so marked as in the first group, but the actual serum-iron levels were not so high. It is difficult to say whether this rise in serum-iron was due to increased iron absorption following on the intake of food or whether it was due to mobilization of iron already stored, but it is interesting to note that in a series of balance experiments Fowler and Barer (1937) found that, while their patients were receiving iron intramuscularly, the absorption of iron from the bowel increased and less iron was excreted in the faeces.

In these two groups of patients treated with ferrous and ferric iron the amount of iron passed in the urine also showed widely different results. Patients given ferric iron excreted nearly 10 times as much iron as those given ferrous. Vannotti and Delachaux (1949) found similar results in rabbits after injection of radio-active ferrous and ferric salts. In view of our results with smaller doses of intravenous iron we had expected that, following the administration of such large doses of iron, a greater percentage of injected iron would be lost in the urine. With smaller doses we found that as much as 5 per cent of the injected iron was excreted, whereas the actual percentage lost in each group of the present series was 1·1 per cent and 0·1 per cent. Moreover, if we follow the blood and urine curves, it will be seen that no further iron was excreted in the urine when the serum-iron was 800 μg. per cent and 540 μg. per cent in each group. We have frequently observed excretion of iron at both these levels in patients receiving small, but more rapidly administered, daily injections. Thus one is led to conclude that there is no fixed renal threshold for iron and excretion occurs only when the body is unable to deal efficiently with the amounts presented to it. Apart from the actual amount and the valency of the iron injected, the rate of administration also plays a part and, as we have already shown, the degree of iron deficiency in the body has some controlling influence.

With regard to the intestinal excretion of iron, Crawley (1952) carried out similar balance experiments and came to the same conclusions as we have, namely, that there was no evidence to suggest excretion of iron into the bowel as a result of the injection. The amount passed in the faeces per day appeared to depend more on bowel action.

From the foregoing one might be led to conclude that therapeutically ferrous iron had an advantage over ferric. The former does not circulate so long in the blood, is more quickly taken up by the tissues and is less readily excreted. Experimental work, however, shows that ferrous salts are best in tissue-iron deficiency, but less effective for haemoglobin synthesis (Vannotti and Delachaux, 1949) and in anaemic rabbits the improvement in the haemoglobin is more rapid with ferric salts. One would, therefore, be inclined to expect a more rapid improvement in the maternal haemoglobin with ferric iron, but at the same time a slower transfer of iron to the foetus. From a study of only 6 patients it is impossible to come to any conclusion as regards this, but it is interesting to note that the most severely anaemic patient with the hypercellular marrow in Group II showed the most marked response to treatment. In her case the haemoglobin rose from 5·0 g. to 6·5 g. per cent in a week. It may be that in the iron deficiency anaemias, in contra-distinction to the experimental anaemias of rabbits, the rate of haemoglobin regeneration depends to a greater extent on the actual state of the bone-marrow rather than the form of the iron administered.

Before concluding this study on the metabolism of iron in pregnant women, a clinical assessment of this method of administering iron by drip infusion should be made. In none of the cases studied above was any severe reaction noted. One patient developed a local thrombosis of the vein, which did not cause any alarm, and with the exception of the patient with severe anaemia, all were allowed home as soon as the balance experiment was finished. From these results it seemed at first that we had a useful method of combating iron deficiency in women, who for various social reasons were unwilling to stay any length of time in hospital, and a further 3 anaemic women were similarly treated. Two responded well but the third developed a severe reaction and the infusion had to be discontinued after 250 mg. of ferrous iron had been given. The initial serum-iron had been 50 μg. per cent and no stainable iron was present in her marrow, which was normoblastic. Two hours later, on stopping the drip, the serum-iron had risen to 410 μg. per cent and only a trace (40 μg.) of iron had been passed in the urine. Reference to Fig. 2 will show that these figures approximate closely to those found in patients with no reaction. There is little doubt that this patient was a case of iron deficiency anaemia. She eventually responded to smaller divided doses of intravenous iron without any untoward effect.

The cause of her reaction is not apparent. It may be that the iron-binding capacity of her

serum was deficient. On the other hand the reaction may have been related to an altered colloidal state of her plasma with resulting alteration in the stability of the injected material. We have discontinued this method of administering iron by massive drip infusions until more is known of the transport of these materials in the blood stream.

Summary

Six cases of iron deficiency anaemia in pregnancy have been treated by massive drip infusion of iron, each receiving the equivalent of 1 g. of elemental iron intravenously over a period of 8 hours. Three received a saccharated oxide of ferrous iron and 3 a ferric compound of the same type.

Only a small proportion of the iron, 1·1 per cent in the case of the ferric compound and 0·1 per cent with the ferrous salt, was excreted in the urine.

None of the iron appeared to be excreted by the bowel.

The average maximum serum-iron level in the group treated with the ferrous salt was 1·59 mg. per cent, compared with a maximum of 3·75 mg. per cent after the ferric compound. Ferrous iron appears to be taken up more easily by the tissues. Haemoglobin regeneration depends more on the state of the marrow than on the type of iron injected.

Although the therapeutic result was satisfactory in these 6 cases, severe reactions have occurred in other patients treated by this method and it cannot be recommended for routine use.

Acknowledgments

I am grateful to Dr. John Hewitt in whose wards this investigation was carried out and to Dr. W. G. Millar and the nursing staff for their cooperation. My thanks are also due to Dr. A. D. T. Govan, Director of Research, for his helpful criticism in the preparation of this paper.

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THERAPY IN THE MEGALOBLASTIC ANAEMIAS OF PREGNANCY

BY

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IN the past 20 years there have been many surveys of pernicious anaemia of pregnancy and its response to treatment. Close scrutiny of the literature, however, shows that almost all of the reports deal with the treatment of the patient in the puerperium. In Davidson, Davis and Innes' series of 16 cases (1942) only 2 were treated antenatally. Stevenson (1938) saw 5 of her 30 cases before delivery and, in an even larger series of 45 patients (Thompson and Ungley, 1951), all but 7 were in the puerperium. Callender (1944) reported on 25 cases, but did not state how many were seen before labour. Excluding her series and others where no details are given, there are reports of 114 cases in this country and only 20 have been treated during their pregnancy (Lescher, 1942; Davidson, Girdwood and Clark, 1948; Holly, 1951; Israëls and Da Cunha, 1952). There is thus little information regarding the efficacy of the various forms of therapy in the antenatal period.

The present report deals with 37 cases of megaloblastic anaemia of pregnancy. Of this number it was possible to study the effects of the various forms of treatment over a considerable period in 19. The remainder went into labour before treatment could be commenced. In addition, 5 cases of Addisonian anaemia controlled by vitamin B_{12} were available for comparison.

METHODS

The diagnosis of megaloblastic anaemia of pregnancy was made after sternal puncture in 26 of the cases. In the remaining 11 patients typical megaloblasts were found in the peripheral blood. Throughout treatment daily reticulocyte counts were made and blood counts and haemoglobin estimations carried out at bi-weekly or weekly intervals, depending on the severity of the anaemia. The haemoglobin readings were made in a photoelectric colorimeter. Serum-iron estimations using the method of Sven Dahl (1948) were carried out in selected cases.

The reticulocyte responses were compared with those found in Addisonian pernicious anaemia (Riddle, 1930). Following the plan adopted by Thompson and Ungley (1951) in their series of pregnancy anaemias, the response was assessed as "good" when it was more than two-thirds the average maximum given by Riddle, "moderate" when it lay between two-thirds and a third and "poor" when it was less than a third. The erythrocyte increases after 2 weeks therapy were also calculated and compared on a similar basis, with the standards laid down by Ungley (1949) for vitamin B_{12}. In this case the dosage was taken as equivalent to 80 μg. As Thompson and Ungley (1951) have already pointed out neither of these methods is entirely satisfactory, but they form a fairly convenient basis for comparative analysis.

To save repetition marrows are described as "active" when the percentage of normoblasts present is not markedly reduced and the process of maturation not obviously slowed. On the other hand a marrow is said to be "inactive" when it shows a reduction of all the erythroid elements, both megaloblastic and normoblastic, a failure in maturation and usually an associated reticulum hyperplasia. Marrows predominantly normoblastic with small percentages of doubtful megaloblasts are not included in the series.

General Features

The general impression gained from the literature is that this condition is one of severe anaemia developing late in pregnancy, but not usually apparent till the puerperium. Sepsis is said to be a frequent complication and in most of the reported series a considerable number of cases have required to be transfused. In the present series the anaemia was of a much milder nature. Only 5 patients were ill enough to require transfusion. No deaths occurred in the series. By comparison nearly 50 per cent of Thompson and Ungley's patients (1951) had red cell counts of less than a million. None of our patients fell into this group and the majority had counts between 1·5 and 2 million. Though the anaemia was milder in nature, the mean cell volume showed a distribution very similar to that of Thompson and Ungley (1951). The majority had an M.C.V. greater than normal, but 29 per cent had values which fell within the normocytic and microcytic range.

Response to Treatment

In order to assess the best form of treatment and to compare the results obtained in pregnancy and the puerperium, the series was primarily divided into two groups, one consisting of 19 patients in the antenatal period and the other of 18 patients in the puerperium. These groups were further sub-divided according to whether they received vitamin B_{12}, parenteral liver or folic acid.

Antenatal Patients

(1) Vitamin B_{12}

This group consisted of 5 patients. The average haemoglobin value was 8·9 g. per cent with a red cell count of 2,180,000 per c.mm. They were given vitamin B_{12} for periods varying from 8 to 15 days, the total dose ranging from 300 to 800 microgrammes.

The results were disappointing. Three patients showed an initial improvement, but this was not maintained. The reticulocyte response was good but the red cell increases were only moderate and the macrocytic nature of the anaemia still persisted. No improvement whatsoever was obtained in the other 2 patients and the reticulocyte responses were negligible. The marrows of these 2 patients were quite inactive and repeat sternal punctures after B_{12} therapy showed a further increase in the percentage of megaloblasts with a shift to the left. Both of these patients previously received oral iron therapy and deposits of iron were present in their original marrow smears. Vitamin B_{12} therapy made no appreciable difference to these deposits.

Serial estimations of serum-iron were made in one case showing a partial response to B_{12}. From an initial value of 360 μg. per cent it fell to 50 μg. per cent during treatment.

Further treatment

All proved resistant eventually and in 4 cases other haematinics had to be given. One patient was put on crude liver by injection and showed slow but continued improvement. The other 3 cases were given folic acid and slowly improved. One of them, however, developed a sensitivity rash and ceased to respond. A change to crude liver by injection was made, but without improvement.

Vitamin B_{12} and Addisonian Anaemia in Pregnancy

By way of contrast 5 cases of Addisonian anaemia were observed throughout their pregnancies. All were adequately maintained on 100 μg. of vitamin B_{12} every 4 weeks. The red cell counts remained well above normal and the only change produced by pregnancy appeared to be a slight degree of iron deficiency around the seventh month.

(2) Crude Liver

This second group of 9 antenatal patients were given crude liver by injection for periods varying from 9 to 100 days. The haemoglobin averaged 7·2 g. per cent and the red cell counts 2,320,000/c.mm. Five showed a satisfactory response to treatment and their marrows, though megaloblastic, were fairly "active". No iron could be found in the smears and all had eventually to be given iron therapy.

Resistant Cases

Of the remaining 4 patients, 3 proved resistant and the fourth developed a resistance after an acute attack of otitis media. In every case the

bone-marrow was inactive. All had been receiving oral iron and deposits of iron were seen in the marrows. Serum-iron readings were made in one case and it was notable that the initial high reading of 350 μg. per cent did not alter, while she remained resistant to liver therapy.

After at least 2 weeks liver therapy without any evidence of a response by way of a rise in reticulocytes or an increase in the red cells, 3 of the patients were given folic acid. All showed immediate improvement. For example one had a reticulocytosis of 18 per cent and her serum-iron fell to 80 μg. per cent before delivery. The remaining patient was maintained by repeated blood transfusions while liver therapy was continued and she eventually began to respond on the tenth day of the puerperium.

(3) Folic Acid

Five untreated antenatal patients with megaloblastic anaemia of pregnancy received folic acid. Four were given 20 to 30 mg. daily orally. The remaining patient received 15 mg. daily intra-muscularly. Their average haemoglobin was 8·7 g. per cent and the red count 2,180,000/c.mm. All showed satisfactory improvement. Sternal punctures were performed on 4 patients and, where the bone-marrow appeared less active, the reticulocyte rise was only moderate. Iron deposits were present in the marrow in all 4 cases. This was not surprising since these patients had received oral iron previously. Serial serum-iron readings were made in 2 cases and a marked fall occurred in both after folic acid therapy.

Puerperal Anaemias

(1) Vitamin B_{12}

Three patients in the puerperium were given vitamin B_{12} intramuscularly in amounts varying from 100 μg. to 1·08 mg. Their average haemoglobin was 6·5 g. per cent and the red count 1,810,000/c.mm. Two showed initial improvement with moderate to good reticulocyte and erythrocyte increases, but after 2 months treatment no further improvement occurred and the red count began to fall. As in the antenatal period the M.C.V. remained high. The third patient in the group showed no improvement and had to be transfused.

The bone-marrow was examined in the cases showing a partial response and was found to be fairly "active". Both patients had been previously treated with iron and iron deposits were present in the marrow in small amounts.

Further Treatment

All 3 patients had eventually to be given folic acid. One defaulted but the other 2 were followed and showed considerable improvement. Of these one carried out instructions and reported 3 months after treatment was discontinued. She showed no evidence of any recurrence of her anaemia.

(2) Crude Liver

This second group of 7 puerperal patients with megaloblastic anaemias were given crude liver by injection beginning with an initial dose of 4 ml. followed by 2 ml. daily. Their average haemoglobin value was 6·7 g. per cent and the red count 2,200,000/c.mm. Five showed satisfactory improvement. Their reticulocyte and erythrocyte responses were good. The remaining 2 patients failed to respond to intramuscular liver.

Sternal punctures were performed in 3 of the patients of this group and it is interesting to note that of these the only case who failed to respond had the least "active" bone-marrow. Iron deposits were present in the marrow of one patient, who had received oral iron for a month, but none were seen in the marrows of the other 2 patients whose M.C.H.C. values were low (22 and 23 per cent).

Further Treatment in Resistant Cases

Both resistant cases were given proteolysed liver by mouth and made a good recovery.

The follow up of puerperal anaemias is never very satisfactory. Only 2 patients in this second group treated with intramuscular liver were seen 3 and 4 months respectively after treatment had been discontinued. Neither showed any evidence of recurrence of their anaemia.

(3) Folic Acid

This last group of 8 puerperal anaemias were given folic acid by mouth in daily amounts of

20 to 30 mg. Their average haemoglobin was 6·6 g. per cent and red count 2,040,000/c.mm. Before commencing treatment 4 patients were observed over periods varying from 3 to 16 days. None showed any evidence of spontaneous remission. The reticulocytes rose to 9 per cent in one instance, but at the same time the red count fell by more than half a million. Once folic acid therapy was commenced, very high reticulocyte responses were observed and the erythrocyte increases were all good except in one patient who had been delivered of quadruplets by Caesarean section. Her response was moderate.

Sternal punctures were performed on 5 patients in this group. All were megaloblastic and showed varying degrees of activity. Iron was present in all the marrows except one case whose M.C.H.C. was 26 per cent. Serum-iron estimations were made in another case. Before delivery the value was 340 μg. per cent. On the first day of the puerperium it had fallen to 70 μg. per cent and after 2 days folic acid therapy a further drop to 0 μg. per cent occurred. The M.C.H.C. had also fallen and intravenous iron therapy was commenced. A complete follow-up was made on 4 patients in this group. They were seen 3 months to a year after treatment had been discontinued and all remained well without any evidence of recurrence of their anaemia.

Discussion

Megaloblastic anaemias of pregnancy are by no means rare, but, owing to circumstances largely outwith the control of the clinician, a diagnosis is seldom made early enough to allow the condition to be treated efficiently before delivery. According to Napier (1940), who studied the condition in India, "pernicious anaemia of pregnancy can be treated in early pregnancy but only checked in later pregnancy". The results in the present series suggest that the position is not quite so hopeless. Few reports in the literature deal with pernicious anaemia in the antenatal period and it is difficult to compare the figures quoted with the present findings.

Early diagnosis and treatment have their effect on both the transfusion rate and the mortality rate. Thompson and Ungley (1951) had to transfuse 21 of their 45 patients. Only 5 of the present series were transfused. Sixteen years ago in this hospital Stevenson (1938) reported 2 deaths in her series of 30 patients. Some years later Davidson, Davis and Innes (1942) recorded 2 deaths in a smaller group of 16 cases. In these deaths sepsis and a transfusion reaction played contributory parts. Callender (1944), however, had 3 deaths in her series where anaemia appeared to be the sole factor. In the present series no deaths were recorded.

Though the anaemia in the present series of cases was milder, the general appearance of the cells and the range of their mean volumes were very similar to those reported by Thompson and Ungley (1951). In both series of cases, the blood picture was either normocytic or microcytic in a third of the patients. In these circumstances diagnosis without the aid of sternal puncture is not easy, especially if typical megaloblasts cannot be found in the peripheral blood. In another series, however, we noticed that, after a few injections of intravenous iron, the red cells tended to become macrocytic and, within a few days, typical megaloblasts could be seen in the blood films. We have used this procedure of giving intravenous iron as an aid to diagnosis to advantage in several cases where it was not possible to carry out sternal punctures. One case in the present series is an example. She was admitted to hospital with an unresolved pneumonia of influenzal type. Her blood picture was normocytic and normochromic (Hb.= 6·4 g. per cent, R.B.C.=2·84 million/c.mm., and M.C.V.=80 μ3) but, on account of the degree of anisocytosis of the red cells and some irregularities in the white cell series, a latent megaloblastic anaemia was suspected though not confirmed. Intravenous iron was given and, after a week's therapy, the haemoglobin rose, the red cell count fell and the blood picture had become more macrocytic. Typical megaloblasts were now present in fairly large numbers in the peripheral blood and the diagnosis was obvious. This was confirmed at a later date by sternal puncture.

With regard to the actual treatment of these megaloblastic anaemias, crude liver parenterally is occasionally successful, but many cases prove refractory. Many similar reports are present in

the literature but no attempt has been made to differentiate the refractory group (Davidson, Davis, and Innes, 1942; Miller and Studdert, 1942; Fullerton, 1943; Callender, 1944; Rubie and Calnan, 1949; Thompson and Ungley, 1951). From the present findings it appears that a preliminary examination of the bone-marrow might be of assistance. Parenteral liver would appear to be of little value unless the marrow is "active". If the marrow is "inactive" a response is most surely obtained by administering folic acid.

In temperate climates it is generally agreed that vitamin B_{12} is of little value in the treatment of the megaloblastic anaemias of pregnancy (Bethell *et al.*, 1948; Ungley and Thompson, 1950). A greater degree of success is reported from India (Patel and Kocher, 1950; Chaudhuri, 1951), but even with large doses (10 μg. daily) one of Chaudhuri's series showed a "plateau" effect and had to be given folic acid. More recently a report by Nieweg (1952) from Scandinavia suggests that some cases of megaloblastic anaemia of pregnancy in temperate climates may improve with vitamin B_{12}. In the present series some response was obtained in 5 out of 8 cases, but the end results were disappointing. Cases with inactive marrows showed no response. A change to other forms of therapy was necessary, but one gained the impression that the previous treatment with B_{12} delayed the subsequent response to folic acid.

Better results were obtained in patients treated initially with folic acid. Unlike previous cases treated with crude parenteral liver or vitamin B_{12} the response to treatment was good irrespective of the state of the marrow. Side effects have not generally been reported but 1 of our cases, who had previously been treated with vitamin B_{12}, developed a rash after intravenous folic acid. Mitchell, Vilter and Vilter (1949) noted a rash in 1 of their cases after the use of oral folic acid and with intravenous injection the same patient developed an anaphylactic reaction.

In considering the effects of the various forms of treatment no differentiation has so far been made between the antenatal and the postnatal patient. The anaemia was more severe in the puerperium, but once treatment was instituted the postnatal patient showed a greater and more rapid response. Occasionally a 100 per cent maximal erythrocyte increase was obtained, a feature not seen antenatally. Reticulocyte counts were also higher in the puerperium. Four patients were left without treatment for periods up to 16 days but no sign of a spontaneous remission was observed in that time. Apart from these findings the results obtained with the various treatments were essentially the same, though the response to crude intramuscular liver was probably better in the puerperium.

In addition to specific anti-anaemic therapy all our patients with atypical blood pictures required iron. Where the M.C.H.C. was low, e.g., 26 per cent, no iron could be found in the marrows. In cases where it was normal traces could be seen and in patients previously treated with iron fairly large amounts were present. On giving liver, folic acid and B_{12} the serum-iron levels fell rapidly in those cases showing a response. Patients refractory to parenteral liver showed no change in their serum-iron levels. Delivery produced a sudden drop in the serum-iron levels, and this has already been noted in cases of Addisonian pernicious anaemia after giving parenteral liver (Smith, 1952). The interesting feature is that a similar process occurs here even in patients who are only partially responding to vitamin B_{12}. Obviously the fall is related to the later part of red cell production and occurs whenever new erythrocytes are produced even if treatment induces increasing failure of earlier cells.

In conclusion, it is obvious that folic acid is the treatment of choice in the megaloblastic anaemias of pregnancy and one has, therefore, to consider the possibility of a deficiency of this vitamin as the aetiological factor. A simple dietary deficiency is unlikely (Najjar *et al.*, 1944; Najjar and Barrett, 1945) and other factors such as malabsorption or inability to split folic acid conjugates are probably of more importance. The frequency of intestinal upsets, especially constipation, in the anaemias of pregnancy lends support to this idea (Scott and Govan, 1949). Moreover, experimental work on rats shows that intestinal stagnation can lead to the development of a macrocytic anaemia which only responds to folic acid (Watson and Witts, 1952).

Summary

(1) The response to various treatments has been studied in 37 cases of megaloblastic anaemia of pregnancy.

(2) The value of early diagnosis and treatment during pregnancy is emphasized. Prompt control of the anaemia at this stage improves the prognosis and reduces both the mortality and transfusion rates.

(3) Folic acid is the treatment of choice, but it is advisable to review all cases in the puerperium at least 3 months after treatment has been discontinued.

(4) Vitamin B_{12} may produce a temporary improvement, but subsequently the condition tends to relapse and the marrow picture shows a more pronounced failure of maturation.

(5) Parenteral liver therapy can induce a return to normal, but in many cases no improvement occurred.

(6) Under folic acid therapy all cases return to normal, even when the marrow shows marked immaturity of cells, but in these cases improvement in the peripheral blood may be delayed.

(7) It is suggested from this that folic acid is responsible for the maturation of the earlier stages of red cell maturation, whereas vitamin B_{12} is more concerned with the later phases of the process.

(8) It seems likely that the condition is induced by a failure to metabolize folic acid conjugates and this may be related to altered intestinal function during pregnancy.

(9) A third of the patients reviewed had an atypical blood picture and diagnosis without an examination of the marrow would have been difficult. It was found that a short course of intravenous iron caused the blood picture to become macrocytic and seemed to stimulate the appearance of megaloblasts in the blood stream.

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Protocols giving fuller details of the results of treatment have been lodged with the Keeper, Department of Printed Books at the British Museum.

HYDROCEPHALY AS A CAUSE OF MATERNAL MORTALITY AND MORBIDITY

A Clinical Study of 304 Cases

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HYDROCEPHALY is one of those relatively uncommon but potentially serious complications which tend to crop up in obstetrical practice when the doctor has forgotten that such a condition exists. It is proper, therefore, that attention should be periodically directed to it in the literature of abnormal labour.

In general, hydrocephalus includes all those conditions in which there is an increased volume of cerebrospinal fluid within the skull. In so-called "internal" hydrocephalus, the excess of fluid is within the ventricles: this is the variety which may cause difficult labour. The brain is thinned-out, the cranial bones are imperfectly ossified (thin and membranous) and the sutures and fontanelles may be large and open. The face is relatively small, the brow protuberant and the head globular and enlarged. For practical purposes, the foetal head has become a bag of water, contained within a thin covering of brain tissue and scalp. If this conception of the condition is kept in mind, its treatment is simplified.

The abnormality may be minor, giving rise to no trouble in labour and being diagnosed only after delivery. It may be moderate, in which about 10 to 20 ounces (280-560 ml.) of fluid may produce an enlargement sufficient to cause serious dystocia. It may be major, in which obstructed labour is inevitable. In an extreme case the circumference of the head may measure 30 inches and the quantity of contained fluid many pints.

In order to collect clinical information, the records of the Coombe Lying-in and National Maternity Hospitals, Dublin, covering a period of twenty years (1932 to 1951 inclusive) were studied. During this time, in 121,385 deliveries at all stages of gestation, there were 304 hydrocephalic foetuses, an incidence of 2·5 per 1,000. It is certain that congenital abnormalities in aborted ova and miscarriage foetuses were overlooked, but all those cases of hydrocephaly, which occurred in foetuses at and past 28 weeks' gestation, were recorded. In obstetrical practice, mainly amongst the poorer classes, it is calculated from this study that 2·7 per 1,000 foetuses of 28 weeks and later show this abnormality. The usually quoted incidence of 1·5 per 1,000 is probably too low.

The average age of the patients was 31·4 years and the average parity 4·4. There were 102 primigravidae and 202 multiparae. The average parity of the multiparae was 6·0.

PRESENTATION IN LABOUR

Vertex	.. ..	205 (67 per cent)
Breech	.. ..	89 (29 per cent)
Transverse	.. ..	6 (2 per cent)
Brow ..	.. ..	3 (1 per cent)
Unknown	.. ..	1
		304

Of the 205 vertex cases, 10 were described as persistent occipito-posterior. The incidence of breech was significantly high, even allowing for the number of premature infants. Undoubtedly, hydrocephaly is a cause of breech.

History of Labour

In 182, or 60 per cent of the cases, labour was considered to have been abnormal, i.e., unduly prolonged or exhausting, requiring reduction of the head or operative delivery. In these cases, the operations, which were performed, and the mode of delivery comprised:

Drainage of fluid through suture, fontanelle, hard palate or spinal canal by means of needle, trocar and cannula or plugging forceps 68; spontaneous delivery without reduction of head, but labour regarded as prolonged and difficult 36; breech extraction without reduction of head, but with variable degree of difficulty in its delivery 20; forceps delivery without reduction of head 16; craniotomy by various instruments 13; internal version 11; scalp traction 7; lower segment Caesarean section 3; hysterectomy for rupture 4; external podalic version 2; symphysiotomy 1 and embryotomy 1.

In these cases, the method of delivery after drainage varied (spontaneous, forceps, breech extraction). In 2 of the Caesarean section cases the diagnosis was missed but the degree of hydrocephalus was minor. The third was complicated by placenta praevia. In the symphysiotomy case the diagnosis was missed and forceps were failed.

The remaining 122 cases (40 per cent) had deliveries which were described as "easy spontaneous" and labour had not been prolonged. However, in this group, there were 3 twin foetuses, 2 being second twins; in 2 cases, the scalp had undergone spontaneous rupture with collapse of the head and relief of obstruction; and many of the foetuses were macerated with soft compressible heads.

Fate of Foetus

There were 128 fresh stillbirths, 83 macerated stillbirths, 83 neonatal deaths and only 10 survived to leave hospital. Thus 211 were born dead and 93 alive.

Associated Abnormalities

These included spina bifida 122 (40 per cent), talipes 29, congenital haemolytic disease 5, hare-lip 4, meningocele 3, imperforate anus 3, multiple deformities 2 and deformities of hands 2. Fifty-four foetuses were premature (5 pounds 8 ounces and less) and 5 twin foetuses were affected.

Complications in Pregnancy, Labour and Puerperium

In pregnancy, the following conditions were noted: toxaemia 38, hydramnios 26, accidental haemorrhage 6, hypertension 6, pyelitis 4, placenta praevia 4, syphilis 2, fibroids 2 and diabetes 1. Many of the patients were anaemic. There was a previous history of abortion in 50, of hydrocephalus in 10 and of other deformities in 15.

In labour, the following complications occurred: emergency admissions 48, inert labour 28, long labour outside the hospital 12, fever and threatened rupture on admission 12, rupture of uterus 9, failed forceps and other attempts at delivery outside 9, haematoma of broad ligament 5, prolapse of cord 5, complete perineal laceration 5, avulsion or distraction of symphysis 3, constriction ring 3, prolapse of hand 2. In addition, 35 patients suffered from postpartum haemorrhage and 4 from obstetrical shock. The placenta was manually removed in 8 cases. There was one instance of haemangioma of the placenta. Of the 9 cases of rupture of the uterus, 4 were treated by hysterectomy and recovered, 3 died and 2 incomplete tears were treated conservatively.

Puerperal complications were as follows: morbid 14, puerperal crural thrombophlebitis 12, peritonitis 3, vesicovaginal fistula 3, necrosis of vagina without fistula 3, puerperal sepsis 3, pelvic abscess 2, agranulocytosis 1. There were 9 maternal deaths (summary to follow).

The list of complications recorded above is a formidable one. Several of the patients were in poor condition on admission as a result of long and exhausting labour, anaesthesia, unsuccessful attempts at delivery, lacerations of the genital canal, dehydration and acidosis. When delivery had been accomplished, there were the added risks of postpartum haemorrhage, infection, thrombophlebitis, embolism and fistula formation. Remote sequelae such as prolapse and stress incontinence, pelvic pain and discomfort, menstrual disorders, cervical infection and secondary sterility must have occurred.

No better example can be adduced in ob-

stetrics of a complication which is easily and safely treated, if diagnosed in good time; but which is easily forgotten, easily missed and lethal in mismanagement. In a previous paper, one of us analyzed 77 cases of badly failed forceps. Hydrocephalus was responsible for 6 of these cases in which were recorded: one maternal death, one rupture of the uterus, two threatened ruptures, one haematoma of the broad ligament, three lacerations of the soft parts, two morbid puerperia, one "white leg" and two vesicovaginal fistulae.

Time of Diagnosis

Examination of foetus after birth 120, difficulty with aftercoming head 50, vaginal examination early in labour 46, obstructed labour 19, abdominal palpation 19, investigation of high and free head 16, radiological examination 14, failed and difficult forceps 10, delay in second stage 6, by outside doctor 4.

Even taking into account that about two-thirds of the cases were minor or minor to moderate in size, it is obvious from the above that the condition was frequently overlooked. It is worthy of note that the non-hydrocephalic head of a macerated premature foetus may be mistaken for a hydrocephalus. A few cases were missed on the first vaginal examination. Radiologically, hydrocephalus was overlooked 6 times, but the films were not all directed to the foetus.

Estimated Degree of Hydrocephaly present during Labour

Minor and minor to moderate 209, moderate 81, major 14. In some of the minor to moderate cases, the degree of enlargement was sufficient to cause serious dystocia. These cases may deceive the most experienced obstetrician.

Maternal Deaths

There were 9 maternal deaths, a mortality of 3 per cent. Two occurred before sulphonamides became available and 3 others before the introduction of penicillin. Two of the patients were primigravidae. As many as 8 of the 9 were emergency admission cases and in poor condition. Thus, on admission, the following conditions were noted:

Moribund 1, rupture 2, threatened rupture 2, shock 3, accidental haemorrhage 1, peritonitis 2, laceration of soft parts 2, many attempts at delivery 3, placenta praevia 1, severe toxaemia 1, haematemesis 1.

The single elective admission case had hydramnios, but hydrocephaly was not detected on X-ray examination. After 10 hours' labour, the head was perforated and delivery completed by low forceps. She developed a haematoma in the broad ligament, caused by partial rupture, and died of infection on the 8th puerperal day.

The causes of death in the remaining 8 cases were: puerperal sepsis 2; rupture, shock, peritonitis 2; accidental haemorrhage, shock 1; pulmonary embolism 1; pulmonary oedema 1; tuberculous pneumonia 1.

One patient, in extremis, died on admission. The time of death in the others varied from 2 hours postpartum to the 18th puerperal day.

These fatalities provided sad reading. Failure of, and delay in diagnosis were apparent in all cases. The radiological misdiagnosis should serve as a warning.

Diagnosis

General Remarks

An important point is that the diagnosis of hydrocephalus is not usually easy. It is not merely a matter of laying one's hands upon the pregnant abdomen and of feeling the grossly enlarged foetal head. The degree of enlargement is seldom gross. Likewise, diagnosis by vaginal and radiological examination may be difficult.

There are, however, certain signs which should indicate the possibility of hydrocephalus. Once the possibility has entered one's mind, one is unlikely to miss the abnormality as pregnancy or labour advances or as complications develop. It must be emphasized that these signs are not all diagnostic, but merely suggestive. In order to be helpful, abdominal, vaginal and radiological methods of examination must be carefully performed and the findings cautiously interpreted. On occasions, the best the clinician and radiologist can do is to sound a warning, but when the warning is sounded, the course of labour will be more closely observed.

1. The foetal head, at the brim or at the

fundus, may feel larger than it normally does. Not infrequently, the normal head, in either position, may appear to the hand to be enlarged and may look large on an X-ray film, especially when it lies transversely or is extended. The hydrocephalic head, unless minor, will be unfixed at the onset of labour. The presence of hydramnios is always suggestive of foetal abnormality, but is more commonly associated with anencephalus than with hydrocephalus. In 304 cases here described, it was mentioned specifically in only 26 or 8·5 per cent.

2. The absence of the typical cephalic pole of the foetus: in ordinary palpation, one seeks, consciously or subconsciously, the hard, round and mobile head of the normal foetus. It may not be found if the abdominal muscles are rigid, if the uterus is contracting or if there is hydramnios. When these causes are excluded, however, one might reasonably suspect that there is no normal cephalic pole because the foetus itself is abnormal. This is a sequence of thought which might be encouraged in teaching.

3. Tenderness on palpation over the lower part of the uterus due to distension by the enlarged head.

4. On vaginal examination, with cervical dilatation, it may be noted that the cranial sutures are widened, the fontanelles enlarged and the scalp feeling like "islets of bone in a sea of membrane". But, when the head has been compressed in labour; when it projects tightly through the brim of the pelvis and when the degree of hydrocephalus is not gross, these findings may not be present to a noteworthy degree. In point of fact, with dead foetus, the bones may overlap. Do not be misled by the absence of so-called "crunching" and "crackling" sensations, which, however, may be elicited. "Crackling" may be obtained with a normal head.

5. Hold-up in the course of labour, especially unexpected dystocia in the multipara with good previous history: even the first stage may be slow and tedious or, in the second stage, the head may remain high despite good contractions. It is wise to bear in mind that dystocia advancing to threatened or actual rupture of the uterus may occur before full dilatation of the cervix is reached.

6. Bimanual examination, in labour, may convey a sensation of marked disproportion between the large mass of foetal head and the maternal pelvis.

7. The authors have experience of a case in which a hydrocephalic head of moderate size moulded itself, with good labour, into the cavity of the pelvis. Unexpected difficulty with forceps was then encountered and only after delivery was the true nature of the abnormality recognized. In breech, the condition may not be suspected until there is difficulty with the aftercoming head. Even the normal aftercoming head, above the brim, feels larger than it really is.

8. When the membranes are reported as being still intact in a case in which they might reasonably have ruptured long since. One of us, within a short period, treated two cases of missed hydrocephalus, in which the patients were allowed to continue in long labour outside the hospital because the attendants had believed that the membranes were still unruptured; what had been felt on rectal examination was not intact membranes, but tense and distended scalp.

9. Radiological examination in different cases of hydrocephaly will reveal (*a*) definite and unmistakable signs of the abnormality, (*b*) uncertain signs, but at the same time sufficiently marked to indicate the possibility of minor to moderate hydrocephalus and, unfortunately, (*c*) negative findings. An explanation for some of the last-mentioned cases may be that hydrocephaly can develop rapidly over a period of a few days, i.e., in the interval between an X-ray examination, such as pelvimetry, and the onset of labour. This is a very important point. As noted, radiological technique must be of a high standard.

In summary, then, at least think of hydrocephalus when the findings on palpation of the foetus do not appear to be quite normal; when the head is not engaged at the onset of labour or when it does not descend during labour in the multipara with a good history; when the lower part of the uterus is tender; when unexpected difficulty arises at any time in labour; when vaginal examination of the foetal head indicates an abnormality and when the radiologist sounds a warning.

Treatment

If hydrocephaly is suspected on clinical or radiological grounds, but not confirmed, the patient should be admitted to hospital and the course of labour carefully observed. As soon as progress has ceased, labour has become abnormal. A vaginal examination is, therefore, carried out. If the condition is verified and if the foetus is alive, the bulk of the presenting head is reduced by drainage through a fontanelle or suture line by means of a suitable needle or trocar and cannula. Labour is then allowed to continue to full dilatation and, usually, spontaneous delivery. If the foetus is dead, a scissors or perforator may be used. If hydrocephaly is suspected with breech presentation, forcible attempts to deliver the unreduced head should not be made. The fluid may again be drained by a suitable instrument (see below).

For confirmed hydrocephalus, with cephalic presentation, tap and drainage are performed as soon as the cervix is sufficiently dilated (usually about 1-2 fingers). It is not advisable to postpone drainage until the os is fully dilated because the first stage of labour, with unreduced head, may be slow, tedious, painful and even dangerous. As noted, rupture of the uterus has occurred before full dilatation. The National Maternity Hospital type needle is 8½ inches long and is malleable. Its length enables it to be inserted into the head, no matter how high this may be; at the same time, the other end of the needle projects beyond the vulva. The needle is left in position and the excess fluid drips away under vision. This is important because brain tissue or clot might obstruct the flow. The collapsed head should not be forcibly extracted, especially through an undilated cervix. Delivery becomes much easier if the head has been propelled by the uterine contractions on to the pelvic floor. The ordinary Barnes forceps is useful for extraction, if this should prove desirable. Willett's forceps may be used if steady traction is indicated. Injury of the soft parts by sharp bone should be guarded against.

In breech presentation, labour is allowed to proceed until arrest occurs at the shoulders. Puncture is performed through the base of the skull; through the bone behind the ear; through the foramen magnum; by incision into the cervical spinal canal or through a spina bifida. A gum elastic or silver catheter or plugging forceps, passed upwards into the brain, may be used for drainage.

Occasionally, and with both presenting and aftercoming hydrocephalic heads, aspiration has been carried out through the abdominal and uterine walls (local analgesia; empty bladder; midline approach).

Internal podalic version is not favoured. With the large head, retracted uterus and thinned lower segment, the operation may be positively dangerous. In any event, drainage of the aftercoming head will have to be effected if the obstetrician wishes to avoid undue force. Drainage of the forecoming head is much easier.

Summary

(1) Practitioners readily forget about hydrocephalus and therefore easily miss it.

(2) It may be expected in about 2 to 3 per 1,000 hospital deliveries at or past 28 weeks' gestation.

(3) In 304 cases described here, the presentation was cephalic in 68 per cent and breech in 29 per cent.

(4) Even taking into account that some of the foetuses were small, macerated and compressible, difficulty in labour occurred in 60 per cent of the cases.

(5) Clinical and radiological diagnosis is not always easy, but, if a warning is sounded, the course of labour can be very carefully observed and the significance of failure of progress appreciated.

(6) Points, helpful in diagnosis, are described.

(7) The complications which may occur as a result of missed hydrocephalus are serious.

(8) Treatment by tap or perforation and drainage is usually easy to carry out. It should be performed early in labour.

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POST-MENOPAUSAL ENDOMETRIAL TUBERCULOSIS

An Unusual Case with a Review of Previous Reports

BY

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POST-MENOPAUSAL endometrial tuberculosis is a relatively uncommon condition, and presenting as a pyometra is still more unusual.

CASE HISTORY

The patient, Mrs. H. B., aged 73, was referred to Mr. A. A. Gemmell in September, 1953, complaining since the previous July of discomfort in the perineum, relieved by lying in bed; there were no urinary symptoms. She had been married for 39 years, had had 2 children, the last 36 years ago and her last menstrual period was in 1936. On general examination nothing abnormal was discovered and there was no history of any abnormal bleeding, but on vaginal examination there appeared to be a cystic swelling in the right side of the pelvis. She was admitted to the Women's Hospital, Liverpool, at the beginning of October, 1953. Examination under anaesthesia on 5th October, 1953, still showed a cystic swelling in the pelvis and so the abdomen was entered through a vertical incision. No cyst was found, but the uterine body was much enlarged for her age, felt cystic and its surface was reddened and highly vascular. Total hysterectomy with removal of both appendages was carried out, during which the uterus was punctured and shown to contain pus, and so a drain was left in the centre of the vaginal wound. The patient made an uninterrupted recovery.

PATHOLOGICAL FINDINGS

The specimen appeared large for the patient's age, the surface was inflamed and, on opening it the uterine cavity was found to be full of pus. The tubes were a little thickened, but the ovaries appeared normal. An unusual feature was that the block causing the pyometra was not at the internal os, but was a shelf of endometrium about two-thirds of the way down the uterine cavity. The mucosa below this level and that of the cervix appeared more or less normal.

The histology was as follows:

Uterus. The endometrium was almost completely destroyed and replaced by a layer of tuberculous granulation tissue.

Cervix. There was mild superficial non-specific inflammation.

Tubes. Showed thickening of the wall and a markedly adenomatous pattern of the mucosa. There was chronic inflammatory infiltration but there were no definite tubercles.

Ovary. Normal for the patient's age.

Culture of the pus from the uterine cavity, aerobic and anaerobic, was sterile. As before the sections were seen tuberculosis was not suspected, the specimen was replaced in formalin which vitiated any further bacteriological examination. However, in this case the histological appearances were unambiguous and the bacteriological confirmation so desirable, as stressed by Haines (1951) in younger women, merely an added refinement. Numerous sections were stained and examined for tubercle bacilli, but as usual none were found. Many further sections of the tubes showed various pictures of tuberculous salpingitis. In the interstitial portion there was only a minimal non-specific round-cell infiltration, more laterally there was a frankly tuberculous pattern, while approaching the ampullae there was the so frequently seen adenomatous pattern with only an occasional tubercle. Everything would indicate that in this case infection of the endometrium was secondary to haematogenous infection of the tube in the manner so common in younger women. Sections of the endometrium below the block showed a typical senile pattern with only a very minimal amount of infiltration by chronic inflammatory cells.

Previous Reports

Reports of post-menopausal cases are few and usually give only meagre details. The first are those of Cornil (1888) and of Krzywicki (1888) who described 2 cases each, all with pyometra, and in Cornil's cases tubercle bacilli were discovered in the pus. Buscarlet (1891) refers to a case which is of interest as the diagnosis was again strengthened by finding numerous bacilli in suitably stained sections. Hofbauer and Vassmer, both in 1898, reported cases aged 57 and 51 respectively, who had ulcero-caseous lesions of the endometrium. In 1899 Bass described the case of a woman of 61 who had tuberculosis in association with carcinoma of the corpus uteri, the first of several such cases, and his report was followed by that of Wallart in 1903 and of De Josselin de Jong in 1906 (cited by Ravid and Scharfman, 1940). Goullioud (1913) described a case of ulcero-caseous disease of the endometrium in a woman of 55 who later died from tuberculous meningitis, and in the same year Gördeler (1913) observed a case of apparently primary tuberculous endometritis in a woman 68 years of age. Three further cases of carcinoma of the body in conjunction with tuberculosis were reported by Bertolini in 1921. In 1925 Daniel described in great detail a case from Bucharest and in addition gave an excellent review of female genital tuberculosis, together with a good bibliography. Weibel (1926) reported a case in a woman aged 90. Menniti (1933), Votta (1934) and Soler (1934) referred to cases of tuberculous endometritis in conjunction with carcinoma of the body in post-menopausal women. Two further cases occurring after the climacteric were described by Jameson (1935) and Sutherland in his papers of 1943 and 1951 mentions 7 cases of post-menopausal endometrial tuberculosis with an additional 1 where the cervix only was affected. Other recent references include Ravid and Scharfman (1940), Eichner *et al.* (1942), Eriksen (1947), Luigi (1950) and Duhamel *et al.* (1952). Howell's (1953) case is of tuberculous infection of adenomyosis in a woman aged 55. Thus it can be seen that the number of cases of post-menopausal endometrial tuberculosis described is remarkably few when compared with the vast literature on the disease as it affects younger women.

Discussion

It is extremely difficult to assess the frequency of post-menopausal endometrial tuberculosis, and many of the reports of isolated cases are of little value in this respect. Gördeler (1913) saw 1 case in 4,620 autopsies. Eichner *et al.* (1942) found 1 case in 1,600 postmortem examinations and 38,000 operation specimens seen at Mount Sinai Hospital between 1916-40. Sutherland and Garrey's (1951) paper is the best source of accurate information. In it they describe 7 cases (with an additional 1 where the cervix only was affected) in almost 66,000 admissions to the Glasgow Samaritan Hospital for Women during the 20-year period 1930-49. As the 66,000 patients represent a special group, all having been admitted for some gynaecological complaint and, therefore, not being representative of the general population, it can be seen that post-menopausal endometrial tuberculosis is, to say the least, an uncommon complaint. With regard to the age distribution, the ages of the reported cases range from 46 to 90, almost half being between 47 and 55, that is, during the years immediately after the menopause. The question of age naturally leads to the point as to whether these post-menopausal cases represent a continuation of a disease process present in earlier life, or whether the condition has arisen only in later life. Our evidence on this point is circumstantial, being based on the fertility of the patients, the presence or absence of menstrual disorders in earlier life and whether there is tuberculous disease present elsewhere in the body, either active or healed. Taking the question of fertility, 14 out of 17 cases where this is recorded have had children, the number ranging from 1 to 16, with an average of almost 5, which is not in keeping with the sterility of younger women with tuberculous endometritis. There appears to be no evidence of menstrual disorder in the case histories which are available. Thus in most cases it seems reasonable to date the infection to some time after the climacteric, and Sutherland's case reported in 1943 of a woman of 66 who had unsuspected endometrial tuberculosis bears out the contention that this may occur. If, too, as Daniel so emphasizes, genital tuberculosis is not self-limited, it seems unlikely, though not impossible, that a woman

of 70 could have localized disease for perhaps half a century.

Having thus brought evidence that the endometrial disease arises in later life, the next question is the route by which infection reaches the uterus. During the reproductive years, it is generally accepted that endometrial tuberculosis is secondary to tubal disease caused by haematogenous spread from a focus in lung or intestine. In the present case, the tubal disease was more advanced at the lateral ends of the tubes than at the uterine ends, suggesting that bacilli had passed along to infect the cavity, rather than that infection had spread outwards from the endometrium. Many of the reported cases, of course, had massive widespread disease in which any attempt to discover the precise route of infection would be quite impossible. There are, however, in this matter two important modifying factors which must be considered; firstly, the greatly diminished blood-supply to the atrophying genital organs, and secondly, the absence of the periodic shedding of the uterine mucous membrane in menstruation. The first is, at any rate partly, responsible for the comparative rarity of the condition in older women (together with increasing immunity) and the second is undoubtedly responsible for the florid caseous tuberculosis so often seen when the disease does occur in this age group.

The actual lesion may take one of three forms commonly recognized—the miliary type, the common ulcero-caseous type and the rare hypertrophic or vegetative type. The first, if untreated, will progress towards the second type, and indeed Sutherland's (1943) case is the only one to fall into this category. Most cases are of the ulcero-caseous type, with occasionally, as in the present example, the formation of a pyometra. The hypertrophic type, described well by Daniel, appears either as an intra-uterine mass which grows inwards and encroaches upon the cavity with little alteration in the external appearance of the uterus, or the disease process may extend outwards and cause gross deformity of the organ. There are a few cases described where tuberculosis has been found in conjunction with another disease, usually carcinoma. In parenthesis, it is tempting to remark upon the simultaneous occurrence of carcinoma of the tube with tuberculosis, reported by several authors, and of carcinoma of the colon with tuberculosis, described by Randall and Spalding (1946), but in view of the high incidence of carcinoma of the uterus and of the colon, and of tuberculous salpingitis, it is doubtful if any conclusion worth consideration can be drawn from this.

Signs and Symptoms

By far the most important sign is vaginal bleeding, which if it is properly investigated should lead to the diagnosis being made every time. Next in order of frequency is leucorrhoea, and several authors have commented on it as being "foul" or "foetid". Pain is not a prominent symptom but when present tends to be hypogastric in distribution. Apart from signs and symptoms of chronic infection, one may find discomfort in the perineum (present case) and a bearing-down sensation, or indeed, as in the present case, a notable lack of any specific signs or symptoms.

In discussing the differential diagnosis of the condition, carcinoma of the body is the most important alternative, but others include fibromyomata, endometrial hyperplasia, non-specific endometritis, carcinoma of the cervix and ovarian tumours. The diagnosis is usually made by histological examination of uterine curettings, but it is preferable, if possible, to isolate the bacilli by culture or guinea-pig inoculation, so that if necessary, antibiotic sensitivity tests and typing can be performed.

Radical surgery would appear to be the treatment of choice, as there is no longer any need to conserve the uterus, and there is little likelihood of antibiotics penetrating the advanced ulcero-caseous lesions, so total hysterectomy with bilateral salpingo-oöphorectomy would seem indicated in the vast majority of cases.

Summary

A case of tuberculous pyometra in a woman of 73 is recorded.

The literature on post-menopausal endometrial tuberculosis is briefly reviewed.

The pathology of the condition is discussed, and it is considered that post-menopausal haematogenous spread to the uterus via the

tubes, followed by the disease progressing to gross caseous ulceration is the usual sequence of events.

The signs, symptoms and diagnosis are briefly considered.

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FIG. 1

Illustrating the loculated nature of the pyometra.
(Scale in centimetres.)

POST-PARTUM GENITAL TUBERCULOSIS

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IN recent years an increased interest has been taken in the association of pregnancy and genital tuberculosis. Authentic cases of pregnancy associated with pelvic tuberculosis are very rare. This paper describes 2 such cases and briefly reviews the recent literature.

In the first case genital tuberculosis was discovered 4 days after a spontaneous abortion at the sixteenth week; and in the second case tuberculous endometritis was detected 4 weeks after a premature delivery of a stillborn foetus at the thirty-second week.

CASE REPORTS

Case 1. Mrs. E., aged 21 and a primigravida married 1 year, attended the antenatal clinic on 7th January, 1953. She was then 3-months pregnant. Menstruation prior to the pregnancy had been normal. Her general health was good and routine examination revealed no abnormality.

The following points are relevant in her history:

(1) Her father had advanced pulmonary tuberculosis which had been diagnosed in May, 1951. (He died in March, 1953.)

(2) Since May, 1951 she had attended her local chest clinic as a tuberculosis contact. Repeated X-ray examination of her chest, the latest in November, 1952, had failed to reveal any abnormality. In February, 1952, her Mantoux test, 1 in a 1,000, was positive.

(3) In December, 1951, one month after her marriage, she had been treated as an out-patient at the Westminster Hospital for a urinary infection. At that time she stated that she had lost 8 pounds in weight during the previous 6 months and in view of this an X-ray of the chest had been performed. This was reported as showing old pleural thickening at the right base but when reviewed in the light of subsequent X-ray examinations a small pleural effusion was detected.

On 11th February, 1953 she was admitted to hospital and 4 days later aborted a 16-weeks foetus. She had complained of lower abdominal pain and occasional vomiting for 1 week before admission.

Twelve hours after the abortion, which was complete, her temperature suddenly rose to 105·4° F. with a pulse rate of 120 per minute. High vaginal swabs and a catheter specimen of urine were sterile. A remittent fever reaching 102-103° F. persisted without the development of any localizing signs or symptoms. A chest X-ray taken on 18th February was reported on as follows: "The right pleural effusion has completely resolved since 4th January, 1952. There is pleural thickening at the right costo-phrenic angle. No pulmonary lesion seen." Blood counts showed that a leucopenia had developed, the number of white cells falling to 3,500 per c.mm., 84 per cent of which were polymorphs. Pelvic examination on 19th February showed no abnormality.

In view of the persisting pyrexia associated with a leucopenia further investigations were carried out. The relevant results are as follows:

(1) Erythrocyte sedimentation rate—29 mm. in 1 hour (corrected).

(2) Graded Mantoux tests—1 in 10,000—Negative.
1 in 1,000—Negative.

(3) Examination of vaginal discharge for *Mycobacterium tuberculosis*. A few acid-alcohol-fast bacilli were detected on microscopy in smears taken on 21st, 22nd and 23rd February. Material taken from the vaginal discharge of 22nd February was cultured on Lowenstein-Jensen medium and inoculated into a guinea-pig. On 10th March a preliminary report on the culture revealed that an organism had been isolated which was presumptively *Myco. tuberculosis*. This was confirmed in the final report received on 23rd March. The guinea-pig inoculation also gave a positive result for *Myco. tuberculosis*.

While awaiting the preliminary report on the culture of the vaginal exudate, there was a morning and evening pyrexia of 101-102° F. and she had profuse night sweats. Pelvic examination was normal except that on one occasion, on 10th March, an acutely tender swelling, the size of a golf ball, was felt in the right fornix.

Examination of the foetus and serial section of the placenta failed to show any evidence of tuberculosis.

Three morning specimens of urine were obtained and no tubercle bacilli were discovered on microscopy or culture.

On 5th March, 1953, 16 days after the miscarriage, a further chest X-ray was taken. It was reported on as follows: "Widespread miliary tuberculosis of both lung fields."

In view of these findings the following treatment was instituted on 12th March:

(1) Streptomycin 1 g. daily by intramuscular injection.
(2) Para-aminosalicylic acid 20 g. daily by mouth.
(3) Isonicotinic acid hydrazide 100 mg. thrice daily by mouth.

With this treatment the patient made most encouraging progress. She became afebrile, gained in weight, and the chest X-ray became normal.

She was transferred to a convalescent home on 17th July. In November a further endometrial biopsy was taken. This was negative for tuberculosis both on histological examination and on guinea-pig inoculation. The chest X-ray was again normal and the E.S.R. was 5 mm. in 1 hour.

Comment

It was considered unnecessary and unwise to perform a curettage on this patient after the detection of tubercle bacilli in the vaginal discharge and therefore histological evidence of tuberculosis is lacking. It is considered almost certain that the pelvis was the origin of the miliary spread as a positive vaginal culture was first obtained only 3 days after a normal chest X-ray; and the miliary lesions discovered in the chest 2 weeks later were of an early type.

It is of interest to note that the foetus and placenta showed no evidence of tuberculosis.

Case 2. Mrs. S., aged 21, a primigravida, attended the antenatal clinic when 3-months pregnant. A general examination was carried out and was satisfactory.

On 20th December, 1952, when 32-weeks pregnant, the patient went into premature labour while away from London and was delivered shortly afterwards of a stillborn foetus. Nothing abnormal was noted by the doctor in attendance either of the foetus or the placenta. There was the usual loss of lochia for the first few days but bleeding recurred slightly after stopping a course of oestrogens for suppression of lactation. This bleeding continued until she was admitted to St. Mary's Hospital for curettage on 15th January, 1953. Vaginal examination showed no abnormality.

Pathological report on the curettings: "Tuberculous endometritis." Guinea-pig inoculation was not carried out. The patient was afebrile and apparently well.

Investigations. E.S.R.: 20 mm. in 1 hour (corrected). *Chest X-ray:* Engorged pulmonary vessels and next to the heart's right border a rounded swelling, possibly the glandular component of the primary infection. *Urine:* 24 hour specimen. No pus. No acid fast bacilli found.

Treatment. Streptomycin 1 g. twice weekly with I.N.A.H. 100 mg. twice daily by mouth for 6 months. She was re-admitted on 21st January for a further endometrial biopsy. This showed early secretory endometrium with no evidence of tuberculosis. *E.S.R.:* 3 mm. in 1 hour. Guinea-pig inoculation was negative.

Comment

Positive guinea-pig inoculation is usually required to make a certain diagnosis of tuberculous endometritis. This was not carried out in this case as a second curettage was considered inadvisable; the diagnosis rests therefore on the histology alone.

Discussion

Twenty-four cases of post-partum genital tuberculosis have been reported in the literature since 1940. These cases will not be discussed individually except where there is a particular point to be mentioned.

The duration of the preceding pregnancy varied from 8 weeks to term; 11 cases were associated with abortions, 7 with full-time pregnancies and the remaining 8 with premature deliveries. The age of the patient is not apparently relevant, as in this series it varied from 18 to 40.

From a study of the symptoms in this series it appeared that the cases fall into two main groups. In the first group, of which there are 17, there is an acute febrile illness starting soon after delivery and often with the development of gross pelvic lesions. Miliary dissemination in this group is comparatively common, occurring in 8 of these patients. In the second group, of which there are 9, the symptoms and signs are minimal and there is often no constitutional disturbance. The lesion is diagnosed as the result of investigating some persistent symptom, usually bleeding or abdominal pain. The 2 cases

described in this paper provide an example of each type.

In order to diagnose the condition it is generally agreed that histological evidence alone is not adequate, but that tissue culture and/or guinea-pig inoculation should be positive. If guinea-pig inoculation were carried out it would usually require a second endometrial biopsy, and from this there is always a risk of miliary spread. Direct examination of the lochia on a slide followed by culture is obviously the safest method of diagnosis. The specimen can easily be obtained from the posterior fornix or endocervix with a pipette.

In this series histological evidence of tuberculosis was obtained in 21 cases; 6 of these had positive guinea-pig inoculations. Two were diagnosed on culture alone, and the remaining 3 on the macroscopic appearances at post-mortem. The time interval between the pregnancy and diagnosis varied from a few days up to 2 years. The latter case, reported by Sutherland (1952), is included as all the symptoms started shortly after delivery. Ten of the cases were diagnosed within a month of delivery. The remainder varied from 1 to 8 months.

Eleven of the patients died.

It is difficult to assess from the literature how many of these patients had pre-existing tuberculous lesions, but it is clear that in the majority of the cases there was no previous history of tuberculosis. There was, however, a clear history of contact with tuberculosis and tuberculous infection in the first case described in this paper.

The exact aetiology of this condition is difficult to determine. It is most improbable that tuberculous endometritis exists before pregnancy commences. All the evidence goes to show that once tuberculosis is established in the endometrium the patient is sterile. Since it is known that 50 per cent of cases of tuberculous salpingitis have patent tubes, it is theoretically possible for a patient with this disease to become pregnant. The disease may then become activated by the pregnancy with or without spread to the endometrium.

It is also possible that tuberculosis spreads from a focus elsewhere in the body to the pelvis during the pregnancy. Whether the tuberculosis exists in the pelvis before pregnancy or not, it would appear that, when the condition does flare up, it may result in a premature termination of the pregnancy. This occurred 18 times in the 26 cases described. In 3 of the cases symptoms began before the termination of the pregnancy. In each case the presenting symptom was abdominal pain.

It is not proposed to discuss treatment in this paper. The danger of the empirical use of Streptomycin, however, in treating post-partum pyrexia is well illustrated by the case reported by Herring and King (1950), in which a 5-day course masked the development of genital tuberculosis.

Post-partum genital tuberculosis is a rare condition but is one which should be borne in mind when investigating any case of prolonged post-partum pyrexia or any persistent post-partum symptom.

Summary

(1) Two new cases of post-partum genital tuberculosis are described.

(2) A brief summary is given of another 24 cases of this condition which have been described in the literature since 1940.

(3) The cases fall into two main groups. The clinical features of each group are described, and the aetiology and diagnosis of this disease are briefly discussed.

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We should like to thank Mr. A. C. H. Bell and Mr. Leslie Williams for permission to publish these cases and for their helpful criticism. Our thanks are also due to Dr. B. W. Lacey for carrying out the many pathological investigations required in the first case described in this paper and to Dr. R. D. Tonkin and Dr. D. W. Brooks for supervising the medical treatments.

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ELECTROCONVULSIVE TREATMENT IN PREGNANCY

BY

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PREGNANCY supervening during mental illness raises difficult problems of management and treatment for the psychiatrist. In the past there has been considerable reluctance to submit the pregnant woman who is mentally ill to physical methods of treatment owing to the risk of abortion or foetal injury. Diethelm (1950) regarded pregnancy to be a contraindication to electroconvulsive therapy. Kalinowsky and Hoch (1952), however, stated that epileptic seizures do not give rise to abortion or premature birth in any unusual degree. Burnett (1946) surveyed the relationship between epilepsy and pregnancy. He found that in 16 cases the occurrence of major convulsions during pregnancy led to foetal death in only 1 instance, that being the result of a fall during a fit. Cooper (1952) reviewed the literature on the use of electroconvulsive treatment during pregnancy in mentally ill women and described a case of his own.

A summary of these data is given in Table I.

As far as can be made out, none of the above cases was given electroconvulsive therapy combined with a muscle relaxant. In view of this fact and because of the advanced state of pregnancy at the time of treatment we thought the following case to be of interest.

CASE REPORT

A married woman of 29 commenced a severe schizophrenic illness in 1952. She became depressed and resentful, and felt something was wrong. She suddenly warned her parents that they were in danger, felt she was being watched and hypnotized, and suspected there was a microphone in the house. She became speechless for long periods at a time. She was admitted to the Bethlem Royal Hospital as a voluntary patient on 18th June, 1952. She was noted to be anergic and disinterested, stood about in stiff attitudes, and was preoccupied with auditory hallucinations, refusing to speak or give much account of her experiences. This condition of catatonic stupor responded temporarily to a course of 8 electroconvulsive treatments followed by a full course (40) of insulin comas, but she never recovered fully. After her discharge from hospital she still felt that she was under an evil influence, that people were against her, and that her thoughts were broadcast. She often stayed in bed for no evident reason.

She was re-admitted to Cane Hill Hospital under certificate on 6th May, 1953 when she was found to be 16-weeks pregnant. No physical abnormalities were detected. She was very vague, suspicious and evasive, felt there was a conspiracy against her, and that the food was poisoned. Her behaviour at times strongly indicated auditory hallucinations. Her attitude to her pregnancy was interesting. She either denied she was pregnant or appeared quite indifferent to it. Alternatively she explained away her amenorrhoea as due to "sterilization". She stood about the ward in awkward constrained attitudes gazing vacantly into space, refused to occupy herself in any way or to interest herself in preparations for the baby. She refused to be bathed or weighed and when approached to carry out routine antenatal examinations became actively resistive so that sedation sometimes became necessary. Once she absconded from hospital and tried to walk home in her slippers.

Because of her earlier temporary response to electroconvulsive therapy the patient was given 6 treatments from the 28th to the 31st weeks of pregnancy. The treatments were given twice weekly using a Strauss-McPhail machine. Modification of each fit was secured by the intravenous injection of 0·2 g. pentothal mixed with 15 mg. Brevedil E (Suxethonium), 30 seconds before the application of the current. Careful observation revealed no uterine contraction either during or following each convulsion. The patient's mental state improved temporarily so that she was able to occupy herself and go out on parole with her husband although still remaining deluded and hallucinated. She had an uneventful labour on 1st October, 1953, and was delivered of a full-time normal female child weighing 7 pounds (3·5 kilograms).

TABLE I

Authors	Age	Parity	Stage of pregnancy months	No. of electro-convulsive treatments	Clinical response	Outcome of pregnancy
Thorpe, 1942 ..	23	(2)	4½	13 (in 6 weeks)	Recovery	F.T. uncomplicated
Polatin and Hoch, 1945 ..	33	(2) (1st breech)	3½–4	6	Recovery	F.T. uncomplicated
	27	(1)	7	10	Unchanged	F.T. uncomplicated
Gralnick, 1946 ..	31	(5) incs. 2 abortions	1–5	24 (plus insulin treatment)	Worse	Macerated foetus at 9th month
Simon, 1948 ..	36	Not stated	4	6	Recovery	Child died 2 days post-partum. "Stormy and toxic pregnancy."
	25	(1)	3 and 8½	10+4	Improved	F.T. uncomplicated
	25	(1)?	6–8½	13	Improved	F.T. uncomplicated
Block, 1948 ..	30	(1)	5–9	30	Recovery	F.T. uncomplicated
Kent, 1947 ..	35	(4)	3–4	16 (plus 50 days insulin treatment)	Improved	Abortion 4th month
	31	(2)	6	26	Improved	Caes. section. Baby weighed 6 pounds
	33	(4)	5–7	20 (plus 90 days insulin treatment)	Unchanged	F.T. uncomplicated
Cooper, 1952 ..	28	(1)	8–9	9	Unchanged	F.T. uncomplicated

The puerperium was normal, but her mental state rapidly deteriorated, she wandered about, was uncommunicative, stripped herself and was, at times, irrational and aggressive in her behaviour.

DISCUSSION

It appears that the administration of electrically induced convulsions during any stage of pregnancy does not materially increase the risk of foetal death. In the 12 cases surveyed the total number of treatments varied from 6 to 30. An abortion at the 4th month and a macerated foetus at the 9th month occurred in 2 cases in which the electroconvulsive treatment was combined with insulin. In another case, however, a normal delivery followed this combination. In the 2 cases in which foetal death occurred it is noteworthy that the convulsions were administered in the first 5 months of pregnancy. From this, it would appear that electroconvulsive therapy administered early in pregnancy, or combined with insulin, may well increase the risk of foetal injury.

In the case in which a neonatal death occurred shortly after delivery the pregnancy was described as "stormy and toxic". The electroconvulsive therapy, therefore, may not have been responsible for this outcome.

Modern techniques for the administration of electrically induced convulsions utilize muscle relaxants to modify or "soften" the tonic and clonic contractions. Besides reducing the risk of fractures and dislocations in the patient, the degree of anoxia occurring during the fit can be reduced by the use of an oxygen re-breathing bag in the phase of postictal coma. It appears to us therefore, that this regime, by avoiding any severe degree of maternal and consequently of foetal anoxia, is specially indicated in pregnancy.

Summary

The literature on electroconvulsive treatment in mental patients during pregnancy has been briefly surveyed and an additional case reported.

The administration of electrically induced convulsions does not increase the risk to the foetus unless given early in pregnancy or in association with insulin treatment.

This is consistent with our present knowledge of the effects of epilepsy on pregnancy.

Our thanks are due to Dr. Alexander Walk for helpful criticism and advice.

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RADIOIODINE TESTS IN A CASE OF STRUMA OVARII

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SINCE Boettlin in 1899 first described the presence of thyroid tissue in ovarian cysts, many cases of struma ovarii have been reported, mainly in Germany and America. In this country only 3 could be found in a survey of the literature covering the past 25 years.

REVIEW OF THE LITERATURE

It is interesting to note that the medical histories reveal no characteristic syndrome; this perhaps is because such aberrant tissue is found mainly in teratomata (MacLeod, 1932), where its amount varies according to different authors. Age above 40 years appears to be the only constant factor. Ascites is present in many cases, and disappears when the cyst is removed (Cachera and Darnis, 1948). There is one report of a case, by Baskin and Counseller (1951), in which hydrothorax was present in addition. Wynne, McCartney and McClendon (1940) report the incidence of struma ovarii, according to the average of five observers, to be 11·6 per cent of teratomata, whilst some have been found in larger cysts—pseudomucinous cystadenomata (Lochrane, 1933). Malignancy occurs to the extent of 5 to 6 per cent (Emge, 1940), and metastases may develop in bone, in the same way as those of the thyroid gland itself. It was not until Moench in 1929 wrote his paper expressing the opinion that thyroid hormone secretion could be produced by some struma ovarii, that attention was drawn to this possibility. Since then, several cases of thyrotoxicosis due to struma ovarii have been reported; McGarrity and Dodson (1948) quote as many as 5 per cent in a survey of 180 cases. Dionisi and Ferraris (1945) described a case in which thyrotoxicosis did not disappear after partial thyroidectomy, and it was only when an ovarian cyst, which proved to be a struma ovarii, was removed later, that the toxic manifestations disappeared. In this, and other such cases reported, studies of the basal metabolic rates showing a rise before and a fall after ovarian cystectomy have proved that the thyroid tissue in the ovarian cyst was responsible for the clinical signs of thyrotoxicosis. In 1933, Plaut reported 3 cases of struma ovarii, and showed the presence of iodine in the ovarian thyroid tissue.

The introduction of the radioiodine tests for the estimation of thyroid metabolism in recent years has provided a means by which the investigations of earlier workers can be carried one step further. After the removal of a struma ovarii in one patient, Perlmutter and Mufson (1951) found that the thyroid gland had not fully taken over its secretory functions till the sixth week after the operation. We have made somewhat similar observations on another patient.

CLINICAL HISTORY OF PATIENT

The patient was aged 38 years, married, para 2+0, the younger child having been born in 1944, since when involuntary sterility had existed. In 1948 she had attended the sterility clinic at the Postgraduate Medical School of London, and the case records show that no

abnormal masses were found on vaginal examination at that time.

Dyspareunia existed, however, and gradually became worse with the result that she presented herself again at the out-patient department. Vaginal examination at this time revealed the presence of a solid smooth painless and mobile mass, about the size of an orange, behind and to the right of the uterus. The uterus was normal in size, but pushed forward and was somewhat limited in mobility because of the mass behind. No other abnormalities were found.

At laparotomy, a right-sided multilocular ovarian cyst was found, which was freely mobile. The cyst was removed. The patient made an uneventful recovery.

The pathological report stated that the cyst (120 mm. × 85 mm. × 75 mm.) was histologically a teratoma, containing a predominant amount of thyroid tissue, and remnants of ovarian tissue (Fig. 1).

It was at this stage that the idea of investigating the thyroid metabolism occurred. Before beginning the radioiodine tests, the patient was examined for evidence of abnormal thyroid activity, but nothing unusual could be found in the medical history.

Comments on the Radioiodine Tests (Table I)

On the first test (12th post-operative day) the thyroid uptake is at the upper limit of normal. At the 3rd, 5th and 6th weeks the uptake is clearly excessive. By the 11th week the thyroid uptake is again merely at the upper limit of normal, and by the 19th week it has returned to a mid-normal value. Between the 3rd and the 11th week, the total urinary excretion is low, and the renal clearance of iodide appears depressed, particularly at the 6th and 11th weeks, by which time the thyroid uptake is approaching normal.

These are the changes that would be expected after subtotal thyroidectomy and imply that the ovary was her main source of thyroid hormone. Immediately after operation, the residual thyroid is stimulated by a rise in T.S.H. due to a fall in thyroid hormone secretion, so leading to hyperplasia of the residual thyroid tissue until the hormone store and its output is restored. During this phase of thyroid hyperplasia, the thyroid uptake is avid. But compensation has evidently been established by the 19th week. The previously impalpable thyroid became palpable for the first time in the neck about the 5th week.

Summary

A case of struma ovarii is reported. The literature dealing with the hormonal activity of this aberrant thyroid tissue is surveyed. In this case, it is shown, by means of radioiodine tests, that the struma ovarii was functioning as normal thyroid tissue in conjunction with the thyroid gland, and that, when the former was removed, the thyroid gland had to hypertrophy before resuming full activity again.

We wish to thank Professor J. C. McClure Browne for his kindness in allowing us to publish this case.

Table I

Radioiodine Test Results

Weeks Post-op.	Urinary Excretion of I^{131}				Derived Indices*	
	0–8 hrs.	8–24 hrs.	24–48 hrs.	0–48 hrs.	(a) Thyroid uptake	(b) Renal Clearance of Iodide
					log T	Ku†
1½	44·8	8·5	0·1	53·4	0·996	13
3½	26·0	0·1	0·1	26·2	2·999	c. 40 (?)
5½	20·2	0·8	0·8	21·8	2·061	8
6½	14·6	3·7	2·7	21·0	1·258	5·5
11½	18·3	6·3	1·1	25·7	1·053	3·5
19½	37·7	16·3	1·2	55·2	0·623	7·8
(Normal ranges)					(0·5–1·1)	(5–12)

* Indices derived as detailed in Fraser *et al.* (1953).

† Percentage E.C.F. iodide excreted in urine per hour.

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FIG. 1

Photomicrograph of a section of the cyst, showing typical thyroid-looking tissue. ×120.

MALIGNANT NEOPLASMS PECULIAR TO FOETAL AND INFANT LIFE WITH A REPORT ON TWO CASES

BY

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MALIGNANT tumours may be classified according to tissue of origin, histological appearance, predisposing cause or age of onset.

Three malignant neoplasms occur during foetal and infant life which are exceedingly rare in the adult, namely:

1. Retinoblastoma,
2. Neuroblastoma, and
3. Nephroblastoma or Wilms tumour.

The conditions of origin and clinical course of these diseases differ from those of tumours of the adult. Retinoblastoma and neuroblastoma have many points in common both in structure and in origin, while nephroblastoma is a unique tumour bearing no resemblance to the others. Many other types of neoplasm are encountered in early life but are not confined to it, sarcoma being by far the most commonly reported.

RETINOBLASTOMA

Retinoblastoma with secondary deposits at birth is an unusual finding and presents some interesting points for clinical study as the following case illustrates.

An unmarried woman aged 29 years was admitted to hospital on 20th June, 1949 in premature labour in the 32nd week of her first pregnancy. She complained of increasing abdominal discomfort from the 29th week of pregnancy onwards. On examination she was found to have hydramnios of marked degree. X-ray examination showed a single foetus with the head presenting. No foetal abnormality was detected. Spontaneous delivery occurred 12 hours after admission.

Description of Infant. The infant was of male sex and 5 pounds in weight. Heart beats were audible following delivery. A few respiratory movements were observed and the infant died.

As shown in the accompanying photographs (Fig. 1) there was a large tumour occupying the left half of the face. It was surmounted by the greatly distended palpebral fissure of the left eye, through which the tumour was fungating. The opaque cornea of the affected eye was partly covered by the upper eyelid. The skin overlying the tumour was stretched, shiny and discoloured. The mouth and nares were displaced to the right side, and were grossly distorted and occluded. The tumour was of soft consistency. The surrounding skin was normal in appearance.

There were 2 nodules in the skin of the mid third of the left thigh on its anterior and medial aspects. The larger nodule was 2 cm. in diameter. There were 3 flat nodules in the skin of the abdominal wall each 1 mm. in diameter.

The general physical examination of the infant was otherwise without significance.

Postmortem Examination

Head. On sagittal section as shown in the accompanying photographs (Fig. 2) a large necrotic tumour, greyish red in colour, was found to be occupying the left orbital cavity. The bony margins of the cavity were not definable. The tumour was bulging forwards beneath the circumorbital tissues, and posteriorly the malignant tissue had invaded both the frontal and temporal lobes of the brain. The buccal cavity was not involved. The right eye

was normal. No enlarged cervical glands were seen.

Lungs. The lungs were not aerated. In the right lower lobe were 2 firm white metastases 1 cm. and 2 mm. in diameter. In the left lower lobe there was one similar nodule 1 cm. in diameter. The hilar glands appeared normal.

Intestines. There was a metastatic nodule 3 mm. in diameter on the antimesenteric border of the jejunum 2·5 cm. from the duodeno-jejunal junction.

Pancreas. There was a firm bluish nodule 1·5 cm. in diameter attached to the tail of the pancreas.

Lower Limbs. Section of the metastases on the leg showed them to be confined to the skin, and the underlying tissues were not involved.

Microscopic Examination

The primary tumour was unsatisfactory for section owing to necrosis.

Sections were taken from the nodules in the lungs, legs and pancreas. The tissue consisted of large round and ovoid vesicular nuclei, and showed great variation in staining. Practically no cytoplasm was visible.

There was no attempt at rosette formation. Some intercellular fibrils were present, however, and areas of necrosis were scattered throughout the tumour (Fig. 3).

Review of Case

The dominant antenatal feature was hydramnios. The mechanism of production in this case was obscure. If absorption from the foetal tissues plays a part in the circulation of the liquor amnii, then occlusion of the lips by facial distortion may have been the cause. The liquor would therefore be prevented from entering the respiratory and gastrointestinal tracts. In that case the tumour was far advanced by the 29th week of pregnancy and must have originated from an early date when malignant tumours have not been reported—even allowing for all the evidence of rapid growth shown by the tumour.

The tumour of the eye must be considered as the primary tumour for the following reasons: (1) It was by far the largest tumour; (2) It had widely invaded neighbouring structures, even the walls of the orbit and anterior cranial fossa; (3) The position of the various metastases which were blood borne followed the foetal circulation from the eye.

There were nodules in both lungs, these being the most likely sites of implantation for cells carried *via* the superior vena cava from the head and neck. The lungs are not by-passed in late foetal life but receive an increasingly large proportion of the blood leaving the right ventricle. The main flow, however, is through the ductus arteriosus to the descending aorta, and hence there were secondary neoplasms in the distribution of various branches of the abdominal aorta and external iliac arteries. It is therefore reasonable to suppose that metastasizing cells reached the placenta *via* the umbilical artery. However, careful microscopic examination of sections of the placenta failed to show evidence of secondary neoplasia.

The mother's chest was X-rayed after delivery, but no evidence of secondary deposits was found in the lung fields.

In view of the familial and hereditary characteristics of this tumour the mother's family history was investigated carefully, but nothing suggestive of retinoblastoma was found. The father's identity, however, was not disclosed, and his family history was unknown to the patient.

The microscopic appearance in this case is consistent with a highly malignant neoplasm. Proliferation occurred at a low level of differentiation, and there is no attempt at rosette formation. The large nuclei and apparent absence of cytoplasm are typical of the tumour.

Neuroblastoma

Neuroblastoma is a tumour closely allied to retinoblastoma. With its more highly differentiated stage, ganglioneuroma, it is not as frequently encountered as retinoblastoma. These tumours are especially striking because of the number that have produced extensive metastases before birth.

By neuroblastoma is meant a tumour of immature undifferentiated neuroblasts; by gang-

lioneuroma is meant one consisting of well differentiated nerve cells and fibres. The two types are not distinct, as many of these tumours are of mixed structure, and the two names merely denote the poorly differentiated and the highly differentiated members of the same species. The former are rapidly growing and malignant, the latter slowly growing and relatively benign. These nerve cell tumours arise from the ganglia of the sympathetic system and the adrenal gland, and they very rarely occur in the central nervous system.

Report of a Case of Neuroblastoma

On the 8th July, 1949, a 33-year-old woman was admitted to hospital at the 40th week of her pregnancy. Labour was normal and she was delivered of a living female infant on that day. The infant weighed 8 pounds 7 ounces. It remained cyanosed after birth although the airway was apparently clear and respirations were well established. It was therefore placed in an oxygen tent. Five hours after delivery its condition had deteriorated. A palpable mass was noted below the left costal margin. Death occurred 19 hours after delivery.

On postmortem examination an apparently necrosed tumour was found arising from the left suprarenal gland and invading the left kidney. It was spherical in shape and about 5 cm. in diameter. Only the anterior borders of the lungs were aerated. No other abnormality was noted.

Microscopic examination showed an undifferentiated tumour consisting of cells containing round, darkly staining nuclei. These cells were grouped and some of the clusters showed an attempt at rosette formation. Intercellular fibrils were visible, in places condensing to form a well-defined stroma (Fig. 4).

Comment on Case

There were no antenatal features to suggest abnormality in this case. The tumour would not have been discovered clinically if the condition of the infant had been satisfactory, and indeed it was not found on the first examination. It would therefore not have shown itself until later in extrauterine life. Although no metastases had formed, the tumour was of undoubted malignancy as evidenced by the manner in which it had invaded the left kidney.

Microscopically the characteristics were those of an undifferentiated embryoma and, in its more structureless sections, were almost identical with those of round celled sarcoma, though some fields showed attempts at rosette formation.

The cause of death was not clear, and may have been unconnected with the neoplasm.

Discussion

Two conditions must be fulfilled before a case may be classified as a malignant neoplasm of the foetus: (1) The tumour must be of proved malignancy by virtue of invasiveness or the presence of metastases. (2) It must be present at birth.

It is obvious that many of the malignant tumours which become clinically manifest in infancy must have been present at birth in a preclinical form. The time lag between the onset of malignant growth and the appearance of clinical signs will depend on many factors, one of the most important being the site of the primary tumour. A tumour of the eye is likely to show itself at an earlier stage of development than one of the kidney or adrenal gland, and this probably accounts for retinoblastoma being by far the most commonly reported as present at birth.

All malignant tumours arising *in utero* have been found in the foetus of late pregnancy, and there is no known tumour of the embryo, in spite of the fact that in recent years many thousands of aborted embryos have been minutely examined for congenital abnormalities in an endeavour to determine the causes of repeated abortion. This is an astonishing fact when one considers that the early embryo is a mass of actively proliferating and differentiating cells of immature development and multipotent character. The early ovum of course gives rise to chorionepithelioma. This arises from epithelium which gives rise to the secundae and not to the embryo.

It is well known that primary malignant tumours of the mother may give rise to secondary

deposits in the foetus. No case, however, has been recorded of a malignant neoplasm of the foetus metastasizing in the maternal tissues.

Summary

Two cases of malignant neoplasm of the foetus are reported and discussed. Some general observations are made on malignant tumours of the foetus.

I am indebted to Dr. A. C. Counsell, Consulting Pathologist, West Middlesex Hospital, for his kind help. My thanks are also due to Mr. D. M. Stern and Mr. C. W. F. Burnett for permission to publish these cases, and to Mr. D. A. Vinten for the photographs.

FIG. 1
Retinoblastoma of the left orbit with metastases in the skin of the left thigh.

FIG. 2

Sagittal section of skull showing tumour invading brain.

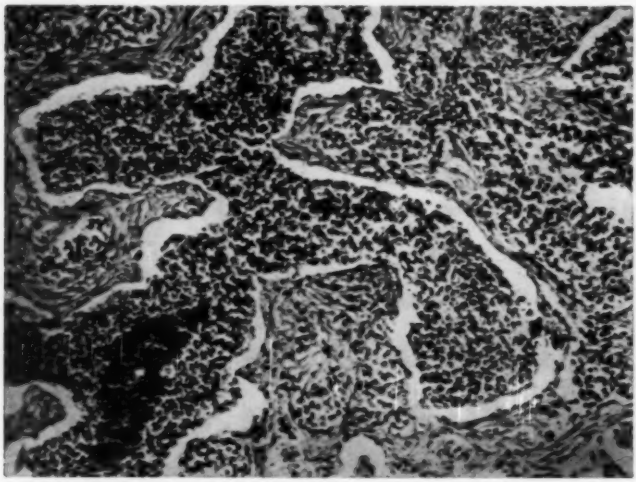

FIG. 3

Section shows masses of cells with ovoid vesicular or darkly staining nuclei with ill-defined cytoplasm in a cellular fibrous stroma. No differentiating features are visible. The central portions of the tumour masses are seen to be necrosed. ×80.

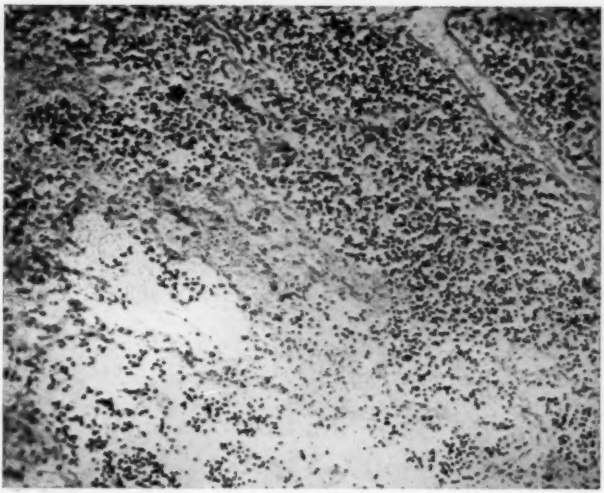

FIG. 4

Section of Neuroblastoma (Low power). Shows masses of cells with small darkly staining nuclei with ill-defined cell outlines. The cytoplasm takes the form of poorly staining fibrillar substance which in places forms a well-defined stroma. ×80.

THROMBOCYTOPENIC PURPURA IN PREGNANCY

BY

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ALTHOUGH case records have recently appeared in the literature with sufficient frequency to suggest that the condition is not uncommon, in 1948 Barnes and Doan were able to find only 6 authenticated cases of thrombocytopenic purpura complicating pregnancy. By 1951, Randak and Danforth found 22 which were acceptable amongst 150 recorded cases, most of the others being of the secondary variety and not true idiopathic thrombocytopenic purpura. The standard textbooks in some instances still regard the prognosis as grave, and as this does not appear to be a true appreciation of the position, the present series has been investigated.

The cause of thrombocytopenic purpura is obscure, but a physiological decrease of platelets has been observed during menstruation (Minot, 1936; Pohle, 1939; Hertzog, 1947) and also during oestrogen therapy (Loftis, 1941; Herbst, 1940; Watson, Schultz and Wikoff, 1947). It may well be, therefore, that many cases of purpura associated with pregnancy represent a response, possibly allergic, to the physiological rise in endogenous oestrogens which occurs at this time.

Congenital purpura may occur in the child, but usually spontaneous remission has occurred within a few weeks (Randak and Danforth, 1951; Landolt, 1948; Epstein *et al.*, 1950; Berkley, 1945; Schefrin and Schectman, 1945; Waters, 1946). Lozner (1953) suggests that either an oestrogen or a platelet agglutinin may be transferred across the placenta to cause thrombocytopenia in the foetus.

CASE REPORTS

During the past 6 years, 5 cases have been encountered in which purpura during pregnancy was associated with thrombocytopenia for which no specific cause was found. They are as follows:

CASE 1

Mrs. L., aged 29 years, had a purpuric rash on her face, neck and shoulders at the 35th week of her first pregnancy, associated with a platelet count of 101,500 per c.mm., which disappeared without specific treatment. This pregnancy was recorded in 1948 (Chalmers, 1948). A year later she became pregnant again and during the third month a purpuric rash again appeared on the face, neck and shoulders. This was still present at the 14th week when she fell down stairs and subsequently aborted without undue blood loss. Neither purpura nor pregnancy has again occurred in this patient. Unfortunately, no blood investigations were practicable during this second pregnancy as the patient lived in a remote part of Scotland 130 miles from a haematological laboratory.

CASE 2

Mrs. G., aged 31 years, had suffered for years from epistaxis and heavy menstrual periods. A purpuric rash appeared for the first time on both legs and the lower part of her trunk at the 38th week of her first pregnancy. Her platelet count was only 50,000 and her clotting time prolonged. On the expected date of labour, one pint of fresh blood was transfused, but labour had to be induced medically a week later. A slow and desultory labour was terminated by forceps delivery, face to pubes, of a large child weighing 9 pounds 2 ounces. This necessitated a wide episiotomy from which bleeding was very free indeed. Blood loss from the uterus was less than 250 ml. and bleeding from the episiotomy was satisfactorily controlled by suture. A further transfusion of one pint of fresh blood was given during the 3rd stage of labour, but 2 days later the mother's platelet count was only 28,000 and that of the child 45,000. The child showed evidence of mild intracranial haemorrhage but subsequently did well. By the 4th day the child's platelet count was 116,000 but that of the mother has remained very low. In spite of this there has been no further purpura during the past 4 years, although a tendency to easy bruising remains. The child has done well.

CASE 3

Mrs. C. J., aged 21 years, was seen on the 9th February, 1953, at the 34th week of her first pregnancy. For some

weeks she had had a purpuric eruption on her face, neck and arms but her thrombocyte count was 360,000. Weekly estimates showed a progressive fall to 114,000 at term. One pint of fresh blood was transfused on her admission in labour at term, and subsequently she had a spontaneous delivery of an apparently healthy child weighing 7 pounds 2 ounces. The total blood loss in labour was 250 ml. and there were no lacerations. After delivery the platelet count rose progressively and on the 9th day of the puerperium was 280,000. The child's count at birth was only 33,000 but this too rose rapidly and on the 10th day was 288,000. The mother's purpuric rash rapidly disappeared and she was free from all evidence of abnormal haemorrhage by the 10th day of the puerperium.

CASE 4

Mrs. G., aged 49 (mother of Case 3), diagnosed her daughter's pregnancy when she observed her purpuric rash because she herself had suffered from purpura during her own only pregnancy in 1932. A purpuric rash developed on her face and arms about the middle of her pregnancy and persisted until a few days after delivery. There had been no undue blood loss at delivery and she had never suffered from purpura at any other time than during her pregnancy. Her platelet count on the 24th March, 1953, was 216,000.

CASE 5

Mrs. M., aged 52 years, stated that at about 25 years of age she had suffered for some years from purpura affecting the legs and the lower part of the trunk. She had a remission lasting about 3 years but had a recurrence during her pregnancy in 1934. Her labour had been complicated by a considerable post-partum haemorrhage and there had been recurrent haemorrhages during the puerperium, in consequence of which she was confined to her bed for about 3 months at this time. There has been no recurrence of purpura since. In August, 1953 her platelet count was found to be 210,000. Her daughter, aged 19, has never shown any evidence of purpura nor has she had a pregnancy. In August, 1953 her platelet count was found to be 360,000.

DISCUSSION

The first case recorded shows the recurrence of purpura in successive pregnancies in the same patient, as previously reported by Vignes and Stiassnie (1921), Hammond (1952), whilst the 3rd and 4th represented the recurrence of the condition during the pregnancies of a mother and her daughter, neither of whom had suffered any purpuric manifestations at any other time. This has not, so far as I know, been previously recorded, but it supports the suggestion of Robson and Walker (1951) that thrombocytopenia may be a hereditary condition. The daughter showed a progressive fall in her thrombocyte count as the pregnancy progressed, but there was a rapid return to normal after delivery. The mother has shown no subsequent abnormality. We thus have 3 patients in whom purpura has occurred in 4 pregnancies, none of whom suffered from purpura at any other time, and in whom there was no undue blood loss at delivery. It would seem that in these cases the purpura can be regarded as almost specific to pregnancy and resulting probably from the increased oestrogen levels to be found at this time. In these women the absence of excessive uterine bleeding was due to control of haemorrhage by the muscular activity of the uterus which is largely independent of thrombocyte function.

Case 2 showed another point of interest. Here there was a history of epistaxis and menorrhagia extending back for some years although a purpuric rash was first observed late in pregnancy. Even so, there seems to be little doubt that this is a case of chronic purpura. Although uterine bleeding was no more than average, there was unexpectedly severe bleeding from an episiotomy. This indicates the importance of the avoidance of operative interference, and particularly of Caesarean section, wherever possible. Epstein *et al.* (1950), however, have recorded the history of a woman in whom Caesarean section was carried out in 3 pregnancies without excessive blood loss.

In both Cases 4 and 5 only a history of purpura during pregnancy has been obtained. In Case 5 the patient stated that she suffered for some years in her twenties from chronic purpura, but that she had a recurrence during her pregnancy following a remission lasting some years. Here the labour was complicated by post-partum haemorrhage and recurrent haemorrhages occurred during the puerperium. In these women, the platelet counts tended, even 20 years after the pregnancies, to be on the low side and it seems reasonable to suggest that here, as in Cases 1, 2 and 3, the higher oestrogen levels occurring in pregnancy were responsible for further depression of the platelet count leading to the appearance of frank purpura. Moir (1953) has described a case in which allergy to progesterone appeared to be the precipitating factor

causing thrombocytopenia, and it may be that, in some instances, progesterone rather than oestrogen is the responsible allergen.

With regard to the children, a platelet count on the 10th day in the first pregnancy of Case 1 was normal. There was severe thrombocytopenia in the child of Case 2, but this rapidly disappeared and in spite of a mild intra-cranial haemorrhage probably due in some measure to the thrombocytopenia, it made a good recovery and the platelet count rapidly rose to normal levels. In Case 3 there was depression of the child's count very much greater than that in the lowest count recorded in the mother, but here also the return to normal was very rapid.

The children of pregnancies reported in Cases 4 and 5 many years after birth showed normal platelet counts, but the former suffered from purpura in her own pregnancy when there was a progressive depression of her count to a low level. There may well be some congenital hypersensitivity to oestrogens in this girl and possibly in the daughter of Case 5 which will only become manifest during pregnancy.

From all these cases it would seem that the following conclusions can be drawn:

(i) That in certain women purpura may occur during pregnancy and at no other time, probably owing to the physiological rise in circulating oestrogens, although the platelet count may be normal or nearly normal in the absence of pregnancy.

(ii) That post-partum haemorrhage is not usually a special risk in these cases since uterine haemostasis is achieved by muscular activity rather than by blood coagulation. Severe bleeding may occur, however, from surgical or traumatic wounds sustained during the course of the pregnancy and they should be avoided wherever possible.

(iii) The use of transfusion of fresh blood as near as possible to the onset of labour should give good protection against severe haemorrhage and should be practised prophylactically in all cases. Where blood transfusion alone is not effective, A.C.T.H. or Cortisone may constitute a valuable adjuvant.

(iv) By the judicious use of transfusion or A.C.T.H. or Cortisone, it should be unnecessary to undertake splenectomy during pregnancy, especially as in chronic cases this operation may be attended by a high mortality.

(v) The prognosis of thrombocytopenic purpura in pregnancy is usually favourable, granted the proper use of treatment to promote remission during labour and the avoidance of trauma.

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A STUDY OF VARIATION IN THE LENGTH OF THE MENSTRUAL CYCLE

BY

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IN examining variation in the length of the menstrual cycle in man the investigator is confronted with difficulties of two kinds. In the first place, it is difficult to record accurately, and over a reasonable period of time, the date of onset of menstruation in a representative group of women. Observations on length of cycle taken from a woman's statement are not sufficiently reliable for statistical examination, and the only reasonably satisfactory data are those specifically recorded for the purposes of an enquiry, and preferably supervised during the period of their collection. Among the most useful data of this kind in the literature are those reported by Foster (1889), Issmer (1889), Pratt, Allen, Newell and Bland (1929), Allen (1933), King (1933), Engle and Shelesnyak (1934), Fluhmann (1934), Scipiades (1935), Gunn, Jenkin and Gunn (1937), and Latz and Reiner (1937). Secondly, even when reliable data are available, it is by no means easy to decide upon a satisfactory treatment of length of cycle. Most women have occasional irregular periods, and in some women the incidence of irregularity is so high that mean length of cycle is of little value. It is therefore not surprising that examinations of length of cycle have frequently been based on pooled data (see Arey, 1939), that is on cycles recorded for a group of women over a period of time. This method, which has also been used in investigation of the menstrual cycle of monkeys (Hartman, 1932), and chimpanzees (Elder and Yerkes, 1936), has the disadvantages that (*a*) the number of cycles contributed to the pool by individual women varies with length of cycle, and (*b*) it does not give an expression of length of cycle for individual women, as required for investigation of the relation of the cycle to variables such as maternal age and parity.

In the present communication we have recorded the menstrual cycle during the 12 months following the birth of a child, and the data are used to examine variation in length of cycle, and its association with maternal age, parity and lactation.

SOURCES OF DATA

For all mothers domiciled in the County Borough of Smethwick whose children were born between 1st April, 1949 and 31st March, 1950, an attempt was made to record the menstrual cycle for one year after delivery. Either on leaving hospital or at the first home visit of a health visitor, mothers were given a calendar on which they were asked to cross off each day of bleeding. This calendar was printed on a child's record card, on which were entered other items of more interest to the mother (such as the weight of the child). Mothers were subsequently interviewed at a welfare centre or at home within 2 weeks of each quarter during the year following birth, at which time the record card was inspected and the menstrual history copied on to another document. These documents provided the data used in the analysis, which is based on the 1,227 mothers of single births whose children survived to the end of the first year.

Mean Length of Cycle

Of the 1,227 women, 197 provided incomplete records of menstruation, and 31 had no menstrual cycle during the year following delivery. Table I gives the distribution of the remaining 999 women according to their mean lengths of cycle. This distribution, as well as the mean cycle length based on all 999 women (30·4 days), is of course considerably affected by the inclusion of women with grossly irregular cycles, and of occasional irregular cycles in the histories of women whose cycles are in general quite regular. A distribution has therefore been prepared after adjustment as follows:

TABLE I

Mean Length of Cycle

Length of Cycle (Days)	Crude Data		Adjusted Data*	
	Number of Women	Per Cent	Number of Women	Per Cent
20 and under	2	0·2	—	—
21	2	0·2	1	0·1
22	5	0·5	—	—
23	6	0·6	6	0·7
24	11	1·1	13	1·6
25	39	3·9	32	3·9
26	60	6·0	61	7·5
27	88	8·8	106	12·9
28	146	14·6	139	17·0
29	160	16·0	154	18·8
30	140	14·0	122	14·9
31	84	8·4	78	9·5
32	69	6·9	49	6·0
33	55	5·5	19	2·3
34	28	2·8	21	2·6
35	23	2·3	15	1·8
36	19	1·9	2	0·2
37	12	1·2	1	0·1
38	4	0·4	—	—
39	5	0·5	—	—
40 and over ..	41	4·1	—	—
Total	999	100	819	100
Mean	30·4	—	28·4	—
Error of Mean ..	±0·2	—	±0·1	—
S.D.	5·9	—	2·8	—

* The method of adjustment is described in the text.

(*a*) Exclusion (on grounds of insufficient data) of 175 women for whom fewer than 5 cycles were recorded.

(*b*) Omission of cycles of less than 16 or more than 40 days from records of the 824 women with at least 5 recorded cycles.

(*c*) Estimation of crude mean length of the remaining cycles for each of 822 women (in 2 cases all cycles were eliminated by (*b*)).

(*d*) Omission of cycles more than 7 days longer or shorter than the crude mean.

(*e*) Exclusion of the 3 women who had fewer than 3 cycles (after (*a*)-(*d*)).

(*f*) Estimation of mean length of the remaining cycles for each of 819 women.

As indicated previously (Gibson and Dougray, 1953) this somewhat artificial treatment is merely designed (*a*) to give means in that selected group of women whose cycles are sufficiently regular to make estimates of their mean length of any value, and (*b*) to make the estimate of the mean more accurate in these cases by excluding occasional irregular cycles.

Table I gives the distribution of the 819 women according to the adjusted mean length of cycle. For all 819 women mean length of cycle is now 28·4 days, and as would be expected both the error of the mean and the standard deviation are considerably smaller than in the case of the crude data.

So far as we are aware only Gunn *et al.* (1937) have previously examined the distribution of a large group of women according to mean cycle length. They gave 28·7 days as the mean length of cycle for 770 women.

Length of Cycle Related to Maternal Age and Parity

Table II shows the association between adjusted mean cycle length and age and parity; for 7 of the 819 women age and parity were unknown. Length of cycle appears to decrease slightly with age, but the relationship with parity is irregular. In view of the small differences involved, these associations are more satisfactorily exhibited by examination of correlation coefficients, which are given in Table III. There is a negative correlation between cycle and age (−0·295) and between cycle and parity (−0·146); but the correlation of cycle with age remains when parity is fixed (−0·259), whereas the negative correlation of cycle with parity is removed (+0·002) when age is fixed.

TABLE II
Mean Length of Cycle Related to Age and Parity

Age (Years)	Parity				
	1	2	3	4 and over	Total
24 and under	28·9	28·9	29·4	—	28·9
	(164)	(67)	(13)	(2)	(246)
25–29 ..	28·9	28·2	28·3	27·8	28·5
	(110)	(102)	(48)	(19)	(279)
30–34 ..	28·3	27·9	28·5	28·4	28·2
	(42)	(61)	(35)	(42)	(180)
35 and over	27·9	27·0	27·7	27·4	27·4
	(10)	(28)	(25)	(44)	(107)
Total ..	28·8	28·2	28·3	27·9	28·4
	(326)	(258)	(121)	(107)	(812)

TABLE III
Correlation between Mean Length of Cycle, Age and Parity

Correlated Variables	Correlation Coefficients	Correlation Coefficients Corrected for:		
		Parity	Age	Cycle
Cycle and Age ..	−0·295	−0·259	—	—
Cycle and Parity	−0·146	—	+0·002	—
Age and Parity	+0·502	—	—	+0·472

It is concluded that the length of the menstrual cycle decreases as age increases (a result previously noted by Gunn *et al.*, 1937), but is unrelated to parity. This may account for the small negative correlation observed by Karn and Penrose (1951) between the period of amenorrhoea (from onset of menstruation to delivery) and age, since it was shown (Gibson and Dougray, 1953) that the correlation between the period of amenorrhoea and age is trivial when length of cycle is fixed. It seems probable that the association between the period of amenorrhoea and age is due to variation in the interval between onset of menstruation and ovulation, and that the period between ovulation and birth is independent of age.

LENGTH OF THE CYCLE RELATED TO LACTATION

Knowledge of the physiology of lactation, and in particular of its control by pituitary and ovarian hormones, made it seem worth enquiring whether there is an association between the menstrual cycle and the history of lactation. It is conceivable (*a*) that involuntary failure of lactation may be due to an endocrine abnormality which might also be manifested in irregularity of the cycle, or (*b*) that voluntary weaning shortly after birth might have some effect on subsequent cycles.

Examination of this matter on the data available is somewhat complicated by the fact that the cycle was recorded for only one year after birth, and hence the longer the duration of lactation the shorter the history of menstruation. Moreover the method by which an adjusted mean length of cycle (our most useful index of menstruation) was calculated for 819 women excludes mothers for whom fewer than 5 cycles were recorded, and hence would be expected to exclude some women because lactation was prolonged.

Table IV, which relates mean length of cycle to duration of lactation (expressed as the total period for which the child was at the breast, whether or not it was also artificially fed), shows that mean length of cycle was recorded for only 56·2 per cent of women who fed their children for more than 240 days. But for shorter durations of lactation there is little variation in the proportion of mothers represented (approximately 80 per cent) in each group. The evidence presented in Table IV suggests that mean length of cycle after the return of menstruation is unrelated to the total period of lactation. It seemed worth repeating the examination using the period of breast feeding without artificial supplements as the duration of lactation. The results obtained by this treatment (Table V) support the conclusion that length of cycle is not influenced by lactation.

It is possible of course that although the duration of lactation is unrelated to mean length of cycle in women with regular periods, it has some effect on the incidence of irregular cycles. The data given in Tables IV and V suggest that this is not the case. For the method by which the adjusted mean lengths of cycle were estimated fairly effectively excludes women with irregular periods, and the fact that the proportion of women so excluded is unrelated to the duration

TABLE IV

*Length of Cycle Related to Duration of Lactation (a)**

		Duration of Lactation (Days)								
		0–	10–	30–	60–	120–	180–	240 and over	Unknown	Total
Number of Women		143	212	189	180	79	73	185	166	1,227
Women for whom mean length of cycle is recorded	Number	119	164	160	143	64	57	104	8	819
	Per cent	83·2	77·4	84·6	79·4	81·0	78·1	56·2	—	66·7
Mean Length of Cycle (days) ..		28·3	28·3	28·2	28·4	28·2	28·3	29·3	—	28·4

* (*a*) Duration of Lactation is the period of breast feeding without and with artificial feeding.

TABLE V

Length of Cycle Related to Duration of Lactation (b)†

		Duration of Lactation (Days)							
		0–	10–	30–	60–	120–	180 and over	Unknown	Total
Number of Women		236	229	176	174	210	55	147	1,227
Women for whom mean length of cycle is recorded	Number	187	191	142	132	139	26	2	819
	Per cent	79·2	83·4	80·7	75·9	66·2	47·3	—	66·7
Mean Length of Cycle (days) ..		28·3	28·2	28·2	28·5	28·6	29·3	—	28·4

† (*b*) Duration of Lactation is the period of breast feeding without artificial feeding.

of lactation (except after 240 days in Table IV and 120 days in Table V) suggests that the influence of lactation on the incidence of irregularity must be slight.

RETURN OF THE CYCLE AFTER PREGNANCY

It has been reported that immediately after the menarche the menstrual cycle is longer (Rork and Hellebrandt, 1940) and less regular (Engle and Shelesnyak, 1934; Larsen, 1947) than in later years and it was thought of interest to consider whether the first cycles established after pregnancy are different from those which follow. Records of the first 5 cycles were complete in 755 of the 819 women for whom length of cycle was estimated, and Table VI gives the means in these cases. Although it is shown above that length of cycle is unrelated to parity, in the present context it seemed worth dividing mothers according to parity. The results indicate that the first cycle is longer and somewhat more variable than those which follow.

SUMMARY

(1) The history of menstruation has been examined in women whose cycles were recorded for one year after the birth of a child. Distribution according to mean length of cycle is given (*a*) for 999 women who had at least one cycle during the year, and (*b*) for 819 whose cycles were sufficiently regular to permit a more reliable estimate of the mean to be made (Table I).

(2) Mean length of cycle decreases with age ($r = -0{\cdot}295$), but is unrelated to parity when the effect of age is removed.

(3) The duration of lactation appears to have no influence on length of cycle.

TABLE VI

Mean Length (days) of the First Five Cycles after Parturition

Cycle Number	Parity						Total	
	1		2		3 and over			
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
1	32·1±0·7	12·3	30·8±0·6	9·2	30·6±0·6	8·3	31·3±0·4	12·6
2	30·0±0·4	7·6	29·1±0·4	6·8	28·6±0·5	6·9	29·3±0·3	7·2
3	29·7±0·4	6·3	28·8±0·5	8·6	28·5±0·5	6·6	29·1±0·3	7·2
4	30·0±0·4	7·1	27·6±0·3	5·4	28·1±0·4	5·9	28·7±0·2	6·3
5	30·0±0·4	6·9	29·3±0·5	8·5	28·0±0·3	4·9	29·2±0·3	7·1

(4) Examination of the first 5 cycles after pregnancy and lactation indicates that the first cycle is longer and somewhat more variable in length than those which follow.

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MATERNAL AND FOETAL BLOOD ESTIMATION FOLLOWING THE ADMINISTRATION OF CHLORAL HYDRATE DURING LABOUR

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THIS investigation is concerned with the transmission of chloral hydrate across the placental barrier, the estimation of chloral hydrate and its allied derivatives trichlorethanol and trichloracetic acid in the maternal and foetal blood (cord blood) and when feasible in the amniotic fluid. It includes 52 unselected pregnant patients and their offspring, who were delivered in the Maternity Ward of the Jefferson Medical College Hospital by the house staff. The transmission of drugs across the placenta has been investigated by Apgar and Papper (1952), Woltz and Zintel (1945) and others. The patients selected for this study attended the out-patient department, the youngest being 16 years and the oldest 36 years. The majority fell in the group between 21 years and 30 years. There were 14 primigravidae and the rest multigravidae. The patient of the lightest weight was 94 pounds and the heaviest was 285 pounds. In this group there were delivered 52 living babies—24 males and 28 females. Table I illustrates some of the complications during pregnancy in the group studied.

TABLE I

Cardiac disease ..	3	Obesity	2
Anaemia	10	Syphilis (proven) ..	3
Varicose veins (previous surgery)	1	Toxaemia (pre-eclamptic) ..	5
Uterine myomata ..	1	Placenta praevia ..	1
Urinary tract infection	1	Rh negative ..	4

Most of the patients were permitted to deliver spontaneously under pudendal block or local infiltration anaesthesia (procain 1 per cent was employed). Table II illustrates the types of deliveries.

TABLE II

Spontaneous delivery	47
Forceps delivery (outlet)	4
Breech (assisted)	1
	52

Procedure: The selected patients were administered chloral hydrate in doses varying from 1·4 g. to 3·1 g. when in active labour. The mode of administration was either oral, oral and rectal, or rectally. The dose and time of administration was carefully recorded and, when the patient was delivered, samples of maternal and foetal blood (cord blood) were taken, and in some cases amniotic fluid was also taken for study, when not contaminated. The specimens taken for analysis were transferred to sterile oxalated tubes which were immediately sealed and sent for examination. The examination included the determination (quantitative) for chloral hydrate and its allied derivatives trichlorethanol and trichloracetic acid.

When chloral hydrate is administered a level is rapidly attained, followed by the oxidation to trichloracetic acid and the reduction to trich-

TABLE III

No.	Dose		Mg./ml. Trichlorethanol			Trichloracetic Acid			Mg./ml. Chloral Hydrate			Time
			Maternal Blood	Cord Blood	Amniotic Fluid	Maternal Blood	Cord Blood	Amniotic Fluid	Maternal Blood	Cord Blood	Amniotic Fluid	
42	1·4	R	3·5	3·0	—	17·0	17·0	—	5·0	5·0	—	15′
6	1·4	R	4·0	4·0	—	5·0	5·0	—	5·0	0	—	16′–30′
26	1·4	R	3·0	3·0	—	20·0	15·0	—	5·0	5·0	—	16′–30′
4	1·4	R	4·0	6·0	—	7·5	Trace	—	2·5	0	—	16′–30′
27	1·4	R	3·5	2·0	—	12·5	4·0	—	5·0	1·0	—	16′–30′
39	1·4	R	1·7	1·7	—	0	0	—	2·5	0	—	31′–45′
30	1·4	R	2·0	3·0	—	5·0	10·0	—	2·5	2·5	—	31′–45′
16	1·4	R	4·0	5·0	—	9·2	4·7	—	4·6	4·5	—	31′–45′
34	1·4	R	9·3	4·3	—	30·0	22·0	—	6·0	14·0	—	46′–60′
35	1·4	R	2·0	15·5	—	14·0	2·5	—	4·5	6·0	—	46′–60′
45	1·4	RO	1·5	Trace	—	2·5	6·0	—	2·5	0	—	46′–60′
49	1·4	R	4·5	5·0	—	20·5	22·5	—	2·0	2·5	—	46′–60′
5	1·4	R	2·3	1·0	—	Trace	Trace	—	0	0	—	61′–75′
31	1·4	R	6·0	15·0	—	15·0	30·0	—	12·5	15·0	—	61′–75′
48	2·0	O	28·0	16·4	—	7·5	5·0	—	7·5	20·0	—	61′–75′
52	1·4	R	9·0	10·6	—	32·0	32·0	—	8·0	6·2	—	61′–75′
24	1·4	R	2·5	1·5	—	17·0	17·0	—	3·0	12·0	—	61′–75′
43	1·4	R	4·5	3·5	—	25·0	25·0	—	7·5	10·0	—	75′–90′
53	1·5	R	3·5	10·0	—	20·0	5·0	—	5·5	5·5	—	76′–90′
36	1·4	R	3·5	4·0	—	7·5	5·0	—	1·25	0	—	1 hr 31′–45′
8	1·7	O	6·0	Trace	—	74·0	33·0	—	37·0	38·0	—	1 hr 45′–2 hr
10	1·0	R	2·3	1·8	—	4·2	8·2	—	7·5	2·5	—	1 hr 45′–2 hr
22	1·4	R	8·6	20·0	—	30·0	37·0	—	15·0	13·0	—	1 hr 45′–2 hr
28	1·4	R	2·0	2·0	—	7·5	5·0	—	12·5	5·0	—	1 hr 45′–2 hr
32	1·4	R	5·0	4·0	—	38·0	42·0	—	8·0	12·0	—	1 hr 45′–2 hr
33	1·0	O	8·0	2·0	—	Trace	0	—	7·5	1·0	—	1 hr 45′–2 hr
17	1·4	R	5·6	5·2	—	32·0	36·0	—	32·0	14·0	—	1 hr 45′–2 hr
23	1·4	R	11·3	1·5	—	11·0	10·0	—	12·5	10·0	—	2 hr–2 hr 15′
40	1·4	R	2·0	2·0	—	27·0	20·0	—	0	0	—	2 hr–2 hr 15′
50	1·4	R	2·0	8·5	—	1·8	14·0	—	8·7	4·7	—	2 hr–2 hr 15′
51	1·4	R	2·1	3·0	—	18·0	12·5	—	10·0	6·75	—	2 hr–2 hr 15′
14	3·1	O	9·7	2·7	—	12·5	15·0	—	7·5	10·0	—	2 hr 16′–2 hr 30′
41	1·4	R	3·1	3·1	—	23·0	6·2	—	12·0	18·8	—	2 hr 16′–2 hr 30′
46	1·4	R	4·4	4·4	—	18·0	18·0	—	6·75	6·75	—	2 hr 16′–2 hr 30′
44	2·3	O	5·5	8·2	4·5	11·0	0	0	48·0	15·0	Trace	2 hr 31′–2 hr 45′
11	3·1	O	22·0	8·0	25·7	Trace	0	0	8·3	6·7	0	2 hr 31′–2 hr 45′
21	3·0	O	5·0	19·5	—	10·0	27·1	—	12·0	11·0	—	2 hr 45′–3 hr
29	1·5	O	3·0	4·0	—	8·0	10·0	—	8·0	2·5	—	2 hr 45′–3 hr
47	1·4	R	5·0	6·5	—	32·0	30·0	—	13·0	8·0	—	3 hr–3 hr 15′
37	1·4	R	2·0	1·0	—	19·0	32·0	—	1·5	3·0	—	3 hr–3 hr 15′
7	1·4	R	4·0	5·0	—	40·0	36·0	—	7·5	20·0	—	3 hr–3 hr 15′
19	2·4	O	2·7	12·8	—	0	Trace	—	14·0	7·0	—	3 hr–3 hr 15′
12	1·4	R	4·8	1·5	—	10·0	10·0	—	2·5	2·5	—	3 hr 16′–3 hr 30′
15	1·4	R	8·0	8·0	—	30·0	35·0	—	0	1·6	—	3 hr 15′–3 hr 30′
	1·4	O			5·5			12·5			0	
3	1·4	R	3·0	4·0	—	5·0	14·0	—	16·0	5·5	—	3 hr 46′–4 hr
2	1·4	R	3·5	3·5	—	25·0	32·0	—	5·0	5·0	—	4 hr–4 hr 15′
25	1·4	R	2·0	2·0	—	15·0	7·5	—	2·5	2·5	—	4 hr 16′–4 hr 30′
1	1·4	R	1·5	5·0	—	17·0	35·0	—	8·0	12·0	—	4 hr 31′–4 hr 45′
9	2·0	R	5·0	10·0	21·0	0	0	0	50·0	45·0	Trace	5 hr 16′–5 hr 30′
13	1·8	O	5·2	6·5	—	10·0	6·0	—	5·0	4·0	—	5 hr 16′–5 hr 30′
20	2·0	O	51·0	11·0	10·0	0	0	0	56·0	40·0	12·5	9 hr 20′
38	1·4	R	1·5	10·0	—	22·5	22·5	—	0	0	—	10 hr

R=Rectal O=Oral

lorethanol. Trichlorethanol is soluble and is potent as a hypnotic, but it is rapidly conjugated with glycuronic acid and excreted in the urine as urochloralic acid; the trichloracetic acid is practically without hypnotic effect and is slowly excreted in the bile. Chloral hydrate, trichlorethanol and trichloracetic acid were determined colorimetrically by the Fujiwara reaction (Butler's method. See Meyer and Smith, 1953.). Table III illustrates the mode of administration of the drug, the dose, and its relation to the time of delivery and the levels obtained in terms of chloral hydrate, trichlorethanol and trichloracetic acid in the maternal and foetal blood and in the amniotic fluid.

Discussion

Fifty-two pregnant women in labour were administered chloral hydrate. It was found that the rectal mode of administration gave more uniform levels. What more, these levels were rapidly attained even as early as 15 minutes after administration. The level in the baby's blood apparently does not bear a direct relationship to the time of crying. In the entire group there was no evidence of foetal narcosis, although our primary aim in this problem did not concern itself with the sedation or hypnotic effect of this drug. Whenever amniotic fluid levels were studied, results comparable to the foetal blood levels were obtained. Although we have observed normal patients and those with complications incident to their pregnant state, we feel that these complications did not interfere with the absorption and the levels attained in both maternal and foetal blood, and in the amniotic fluid. Another factor may be considered, and that is whether the rectal suppository was inserted high or low in the rectum. According to studies it has been stated that, for a stretch of about 5 cm. from the sphincter up, the blood circulation does not drain into the portal system, but enters the general circulation (Quevauviller and Jund, 1951). We were fortunate that our patients were delivered under pudendal block or infiltration anaesthesia, since we did not have the problem of a general anaesthetic to contend with in our investigation. It may also be stated that the age, gravidity and weight of the patients had no bearing on the results.

Conclusions

(1) We observed no deleterious effects following the administration of chloral hydrate to 52 pregnant patients and their offspring.

(2) As soon as chloral hydrate is administered, a level is rapidly attained both in the mother and foetus.

(3) The period of elimination of chloral hydrate is of approximately 8 hours duration.

(4) Trichlorethanol was found with greater consistency in the amniotic fluid than chloral hydrate and trichloracetic acid, and the levels were comparable to those found in the foetal blood.

(5) The complications encountered during pregnancy in the group investigated did not affect the action of the chloral hydrate, and vice versa.

(6) It was found that, when chloral hydrate was administered rectally, the results were more uniform than when administered through the oral route.

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THE EARLY DETECTION OF CANCER OF THE UTERUS

BY

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IN the following preliminary report, two tests, which might be of value in the early detection of cancer of the cervix, are described.

Ideally there should be a simple, reliable cancer screening test which could be performed by every general practitioner, analogous to the tests in use at present for albuminuria and glycosuria. The criteria for such a test should require that it be:

(*a*) Specific for malignant disease.
(*b*) Acceptable to the patient.
(*c*) Technically simple.
(*d*) Economical of time and cost.

There are, of course, several investigations available for the early detection of cancer of the cervix, such as pelvic examination, biopsy, colposcopy, Schiller's tinctorial test, Papanicolaou vaginal smears, the determination of beta-glucuronidase activity and more recently the uptake of radioactive phosphorus. Nevertheless, only the clinical examination, the biopsy and possibly the Papanicolaou vaginal smear have been retained in most hospitals, the other tests having been discarded as being either unspecific or unsuitable. Biopsy, however, though specific, cannot be recommended as a large scale cancer screening test, as it is often unacceptable to the patient, requires instrumental investigation and expert interpretation.

At the Marie Curie Hospital a new approach to the problem of the early detection of cancer of the uterus is being investigated and two tests have been planned which meet most of the above requirements. These are simple chemical investigations, one based on the estimation of lactic acid in the vaginal secretion, the other on the detection of occult blood in the vagina.

TEST FOR THE PRESENCE OF LACTIC ACID

Lactic acid is a normal constituent of the vaginal secretion in women during sexual maturity. Its presence in post-menopausal women is pathological. On the other hand, one of the characteristics of tumour tissue is its capacity for producing lactic acid (Warburg, 1926).

Theoretically, therefore, lactic acid should be absent from the vaginal secretions in women after either a natural or artificial menopause. The presence of lactic acid in post-menopausal women would indicate abnormal metabolic activity suggestive of cancer.

The object of this investigation has been to verify whether the above theoretical considerations are borne out by clinical findings and subsequently to determine to what extent this test for the presence of lactic acid in the vaginal secretion might prove useful as a cancer screening test.

Among the tests for lactic acid we have found the Uffelmann test to be the most satisfactory. Uffelmann's reagent consists of a solution of 2 per cent phenol to which have been added 2 drops of 10 per cent ferric chloride per ml. of phenol solution. The reagent is dark violet in colour and is immediately decolorized by a very dilute solution of lactic acid. The reaction, however, is not specific.

TECHNIQUE FOR OBTAINING THE SPECIMEN

The patient is examined lying simply on her back, the lithotomy position not being necessary. The cervix is carefully swabbed with an orange stick topped with smooth absorbent cotton wool. The swab is then dipped into a test tube containing approximately 3 ml. of Uffelmann's

reagent. If the cotton wool turns violet, this indicates that there is no lactic acid present and the test is negative. If the cotton wool does not turn violet, this indicates that lactic acid is present and the test is positive.

Certain precautions regarding technique and the interpretation of the test are indispensable.

(*a*) A pH higher than 7–8 interferes with the reaction and may render the result unreliable. For this reason no vaginal douches containing Dettol or sodium bicarbonate should be given within 24 hours of the test, neither should the fingerstall be dipped into green soap nor any lubricating agent. Severe infection, bacterial or from trichomonas, must first be excluded as this may reduce vaginal acidity to a considerable extent. It is helpful to determine first the vaginal pH using a wide range indicator paper. In some cases douching with saline during several days may reduce the pH and the test may then be carried out safely.

(*b*) All contact with urine must be avoided. This is particularly important with patients suffering from urinary incontinence or prolapse of the uterus.

(*c*) Though blood as such does not interfere with the reaction, interpretation of the result in patients with heavy bleeding may be difficult. It may be advisable to repeat the test at a time when bleeding has diminished.

(*d*) Very thick, mucoid alkaline secretion from the cervical glands may form a glistening, transparent, water repellent film on the swab and may interfere with the absorption of the reagent and a false positive reaction may be obtained. In the presence of this type of secretion, which is easily recognized by simple inspection, it is preferable to adopt a different technique of lactic acid determination, e.g., the Barker Summerson (1941) method on aspirated vaginal secretion.

(*e*) It has also to be borne in mind that cessation of menses is not necessarily identical with cessation of ovarian activity. Thus the Uffelmann test may well be positive in patients who have undergone subtotal hysterectomy or had a recent natural or radium-induced "menopause" (Goldscheider, 1949) but whose ovaries are still active.

(*f*) The lactic acid test in the vaginal secretion does not give any information as to the presence of metastases.

This method suffers perhaps from the disadvantage that the cervix is not swabbed under visual control and that the reagent is not quite specific, but it is hoped to improve upon the technique in due course.

Clinical Results

In a series of 212 unselected patients, the vaginal secretions were tested for the presence of lactic acid. Forty-eight of the patients were in the pre-menopausal stage and 164 were in the post-menopausal stage. Of the 48 pre-menopausal cases, 9 suffered from cancer of the cervix and 39 from some non-malignant condition. All 48 cases gave a positive Uffelmann reaction (Table I).

Table I

Pre-menopausal Patients

Lesion in Cervix	No. of Patients	Uffelmann Test	
		Positive	Negative
Benign	39	39 (100)	—
Malignant	9	9 (100)	—
Total	48	48 (100)	—

Percentages in brackets.

The results of the test in the women of post-menopausal stage is shown in Table II.

Table II

Post-menopausal Patients

Lesion in Cervix	No. of Patients	Uffelmann Test	
		Positive	Negative
Benign	8	2 (25)	6 (75)
Malignant	51	51 (100)	—
Recurrent after Radium	15	14 (93)	71 (7)
Local healing ..	90	5 (5·5)	85 (94·5)
Total	164	72	92

Percentages in brackets.

This Table shows that of 72 patients giving a positive reaction, 65 (90 per cent) were suffering from malignant disease and 7 patients (10 per cent) had a non-malignant lesion. Among the 92 patients showing a negative Uffelmann reaction, 1 (1 per cent) was suffering from cancer and in 91 (99 per cent) the lesion was non-malignant.

From the preceding tables it will be seen that the lactic acid test performed on the pre-menopausal women was positive in every case and apparently is non-specific in this type of patient. In post-menopausal cases, however, the test appears to possess a high degree of specificity. All the primary, untreated cases of cancer, 51 in number (100 per cent) were positive. Of the 15 recurrent cancer cases, 14 (93 per cent) were positive and in 2 of them the test was positive several months before the recurrence became clinically apparent. The single negative reaction was obtained in a patient in whom the lesion was very haemorrhagic and the interpretation was doubtful. In the benign conditions and in those cancer cases where a local cure had been effected the Uffelmann test was negative in 91 out of 98 cases (93 per cent). Amongst the 7 non-malignant cases showing a positive reaction 1 suffered from stress incontinence, 1 presented a heavy alkaline discharge, 1 was suffering from leucoplakia at the introitus; the remaining 4 had had radium therapy within 5, 2, 2 and 1 years respectively. It is possible that in those 4 cases some lactic acid producing tumour cells are still present and these cases will be followed up very closely.

Test for Occult Blood

One of the earliest symptoms of malignant disease of the uterus is bleeding, either macroscopic or microscopic. Although there is a great number of benign conditions which give rise to some form of haemorrhage, malignancy unaccompanied by bleeding is rare, and irregular vaginal haemorrhage is generally the first symptom of uterine cancer. It is at this stage that the patient goes to see her doctor. Earlier stages usually go undetected. Although some benign conditions such as metropathia haemorrhagica also cause irregular bleeding, such cases usually present a catamenia-like flow and the patient in the intervening periods is usually free from any loss, either macroscopic or microscopic. On the other hand malignant cases almost invariably bleed; even in the apparently clear periods some haemorrhage can generally be detected microscopically.

Theoretically, therefore, cases that do not bleed macroscopically but have occult blood in their vaginal secretions might be expected to be malignant, and those with no occult blood to be non-malignant.

In order to investigate this assumption, a test for the presence of occult blood in the cervical secretion has been performed on 93 patients using "Ames" Hematest tablets, a simple highly sensitive reagent demonstrating the presence of occult blood. The results, as seen below, would seem to indicate that this may prove a useful cancer detection test.

Technique

With the patient lying on her back, a finger, protected by a rubber fingerstall, is introduced into the vagina and brought into close contact with the cervix. The secretions adherent to the fingerstall are spread on a small piece of filter paper. A Hematest tablet is placed on the filter paper and a few drops of water added. An immediate blue discoloration of the underside of the filter paper indicates a positive reaction. It is essential to perform this test before any instrumental investigation has been done or any manipulation carried out which might cause an abrasion of the mucous membrane.

For this investigation the patients were selected. All cases with macroscopic or contact bleeding were excluded for obvious reasons. Moreover no Hematest was performed in women in whom there was reason to suspect occult blood in their vaginae, such as recent instrumental investigation or the presence of large palpable polypi. Neither was the test used in those who had previously undergone radium treatment. As erythrocytes are commonly present in the vaginal secretion after irradiation, the test in such cases would be inconclusive.

The following table shows the results of the Hematest carried out on the day of the patients' admission to hospital.

Table III shows that all but 1 of the malignant cases had some form of haemorrhage. The single malignant case showing a negative reaction

suffered from a copious pyometra and it is possible that the purulent discharge may have interfered with the reaction. Of the 64 benign cases all but 4 had either visible haemorrhage or no bleeding at all. Of the 4 benign patients giving a positive Hematest reaction 2 had a cervical erosion and 2 suffered from atrophic vaginitis. It is interesting to note that both these conditions necessitate early detection and treatment, as many consider them to be of pre-cancerous nature. One case of particular interest concerns a woman of 80 years admitted to hospital for intermittent vaginal bleeding. The Hematest was positive in her "clear" interval. Dilatation and curettage gave no evidence of malignancy, but subsequent hysterectomy proved the presence of a sarcoma.

Discussion

Although it cannot be said that the Uffelmann Test and the Hematest are completely specific, the clinical findings so far prove that they are useful adjuvants in cancer detection and it may be claimed that the presence of lactic acid in the vaginal secretion of post-menopausal women is strongly suggestive of malignancy.

The procedure set forth in Table IV is submitted as a basis for large scale cancer screening.

All the preceding suggestions apply only to symptom-free patients. Any symptom, however slight, warrants fuller investigation.

As far as the criteria for a cancer screening test, as set out in the beginning of this paper, are concerned, both tests answer the requirements to a considerable degree. They compare favourably with any other test in use at present such as the Papanicolaou smear. They are reliable, but much simpler and more economical. Material for both tests can be collected at the same examination.

Summary

(1) The requirements of a suitable cancer screening test are described.

Table III

Condition of Uterus	No. of Patients	Macroscopical Bleeding	Contact Bleeding	No Visible Bleeding	
				Hematest	
				Positive	Negative
Malignant	76	17 (22)	18 (26)	40 (51)	1 (1)
Non-malignant	64	12 (19)	0	4 (6)	48 (75)
	140			44	49

Percentages in brackets.

Table IV

Group	Uffelmann Test	Hematest	Result	Advice
Post-menopausal ..	Positive	Positive	Suspicious	Refer to specialist
	Positive	Negative	Suspicious	Refer to specialist
	Negative	Positive	Probably non-malignant	Control regularly
	Negative	Negative	Satisfactory	
Pre-menopausal ..	Negative	Positive	Probably infection present	Bacteriological investigation
	Positive	Positive*	Suspicious	Refer to specialist
	Positive	Negative	Satisfactory	

* Obvious causes such as recent childbirth or abortion, large polypi or infection must first be eliminated. A regular check must be made at intervals when, normally, there would be no occult blood. Avoid, therefore, performing the test immediately after menstruation or ovulation. If the Hematest is positive on 2 or more occasions, refer to a specialist.

(2) Two simple, reasonably reliable tests have been proposed, the technique described and the clinical observations recorded.

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THE NORMAL POST-MENOPAUSAL ENDOMETRIUM

BY

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THE cyclic changes in the endometrium during the reproductive phase of life, together with the mechanism of bleeding at menstruation, have been extensively studied and repeatedly described. The histological appearances of the endometrium in functional bleeding have also received much attention, and attempts have been made to correlate the endometrial pattern with the occurrence of bleeding. There does not appear to have been a proportionate interest in the histological structure of the post-menopausal endometrium. It seems to have been assumed that the endometrium, like the other genital tract tissues, always undergoes simple atrophic change.

In post-menopausal gynaecological disorders, particularly the occurrence of bleeding, considerable emphasis has been laid on the appearance of the endometrium. The bleeding has been related to the finding of cystic glandular hyperplasia and endometrial polypi. Moreover, the pattern of the post-menopausal endometrium preceding and accompanying carcinoma of the corpus has been observed and interpreted in different ways. In particular it has been suggested that endometrial polypi and cystic glandular hyperplasia are frequent precursors of carcinoma, and that a common aetiological factor, namely the long continued action of oestrogen, is present in these conditions. It must be pointed out, however, that these interpretations have been made without reference to the endometrial pattern in the normal post-menopausal woman.

A survey of the literature reveals that few writers have described the endometrial changes in the post-menopausal phase (Payne, 1937; Novak and Richardson, 1941; Gianaroli, 1947; Speert, 1949; Foix, 1952). Although the individual reports differ in many respects, all are agreed that the endometrium does not always show a simple atrophic pattern. Since these authors report on relatively small numbers the incidence of the various changes which they describe may not be accurate. Similarly they do not deal in any great detail with time relationships, and it is possible that some of the variations in endometrial pattern are associated with residual endocrine activity near the menopause. For these reasons it was decided to analyze the findings in specimens taken from 1,521 patients at periods varying from 1 year to 34 years after the menopause. Care was taken in the selection of the type of case studied and all cases of functional disorder were eliminated. Only cases where the patient was aged over 40 years and with a history of amenorrhoea for at least a year were included in the investigation. In most cases the patient suffered from prolapse, and routine curettage was performed before operation for the cure of prolapse was undertaken. In 1,315 cases no material beyond a little mucus was obtained at curettage. The various patterns found in the remaining 206 cases were as follows:

Endometrial Atrophy

A histological diagnosis of atrophy of the endometrium was based on the finding of a thin mucosa with few, small glands in a fibrous stroma. The diameter of the glands was approximately 0·1 millimetre and the average thickness of the endometrium was 0·4 millimetre. The gland epithelium was low cuboidal in type and inactive in appearance.

Inactive Cystic Gland Pattern

Two varieties of this histological change were found. In the great majority of cases a single polyp was present, and in the remainder the condition was more diffuse. Where a polyp occurred, the size varied considerably, the largest noted being $1 \times \frac{1}{2} \times \frac{1}{4}$ inches. This condition was

diagnosed when the glands showed marked cystic dilatation. The diameter of the glands varied greatly, but was frequently about 1·5 millimetres, only about 4 to 6 such glands being present in the average low power field. The cells lining the glands were flattened and inactive in appearance. The glands frequently contained amorphous material of a mucoid nature, and disintegrating epithelial cells were also present in many cases. The stroma had a loose almost myxomatous appearance with small spindle cells. No structures recognized as spiral arteries were seen, but thin-walled veins and dilated capillaries were present, some of these just beneath the surface epithelium.

Active Hyperplasia

Active hyperplasia of the endometrium was characterized by an increased thickness of endometrium with numerous glands and a very cellular stroma. The glands showed a marked variation in size with dilatation in some, similar to that seen in the active phase of "metropathia haemorrhagica". They were considerably smaller than those seen in the inactive gland pattern, varying in diameter from 0·3 to 0·6 millimetre, the endometrium being up to 5 millimetres thick. In the average case, about 20 glands were present in a low power field. The glands were lined by columnar epithelium with basophil cytoplasm and large nuclei. There was enlargement of the stromal cells, and the cells of both glands and stroma showed frequent mitotic figures. Areas of stromal haemorrhage and necrosis were absent. In some cases the hyperplasia took the form of an almost adenomatous arrangement of the glands.

Proliferative Endometrium

The pattern was similar to that found in the first half of the cycle of a woman of the reproductive era. Mitotic figures were present in this endometrium but it lacked the disparity in the size of glands seen in the previous type. The glands were about 0·2 millimetre in diameter and the average thickness of the endometrium was one millimetre.

Fibro-adenomatous Polyp

The term "fibro-adenomatous polyp" was used to describe a polyp in which the stroma was abundant and had a fibrous structure. The cells were spindle-shaped, and the matrix was homogeneous and hyalinized.

Secretory Endometrium

The appearances in this specimen were similar to those seen during the early part of the second phase of the menstrual cycle in the reproductive years. The glands were serrated and showed prominent sub-nuclear vacuolation.

The incidence of the varying endometrial patterns is shown in Table I.

It will be noted that in the initial analysis hyperplasia and proliferation of the endometrium occurred with remarkable frequency in the 206 cases in which the curettings were examined histologically. But there was a non-productive curettage in a very large number of patients in this group and it is obvious that these must be taken into account in the statistical analysis. It would seem probable that, where no endometrial tissue was obtained on curettage, atrophy or inactivity of the endometrium was present in most instances. If the figures are analyzed on this assumption, then the incidence of hyperplasia and proliferation of the endometrium is reduced from 18·6 per cent to 2·5 per cent. The latter figure is almost certainly too low, and it is likely that the true incidence of an

TABLE I

Incidence of Endometrial Pattern in Curettage Specimens

Type of Endometrium	Atrophy	Inactive Cystic Gland Pattern		Hyperplasia	Fibro-adenomatous Polyp	Proliferative	Secretory
		Polyp	Diffuse				
No. of Cases ..	65	80	8	26	14	12	1
Percentage	31·5	38·8	3·9	12·6	6·8	5·8	0·5

TABLE II

Years after the Menopause in Relation to Endometrial Pattern

Years after Menopause	Atrophic	Inactive Cystic Gland Pattern	Hyperplasia	Proliferative	Fibro-adenomatous Polyp	Secretory
Under 5 years ..	31·8	23·1	27·5	11·2	5·5	0·9
6–10 ..	37·2	53·5	—	2·3	6·9	—
11–15 ..	27·6	58·6	—	—	13·8	—
16–20 ..	24·1	65·5	3·5	—	6·9	—
Over 20 ..	38·1	61·9	—	—	—	—

active endometrium lies somewhere between the figures quoted.

With such a variation in endometrial pattern it might be expected that a relationship to some factor in the patients' gynaecological history would be found. On investigation, however, no direct association was noted between the varying post-menopausal endometrial picture and the age of the patient at the menopause, the type of menopause experienced or the parity or marital status of the woman. The only factor which appeared to influence the findings was the length of time after the menopause when the examination was carried out.

Length of Time after the Menopause

Curettage was performed on patients from 1 to 34 years after the cessation of menstruation. In view of the known endocrine imbalance occurring in the early post-menopausal years it was considered important to relate the length of time after the cessation of menstruation to the endometrial pattern found. The results of this analysis are shown in Table II. It will be seen that most cases of hyperplasia and proliferation of the endometrium occurred in the first 5 years after the menopause. The inactive cystic gland pattern was not so frequent in the early years after the menopause, but thereafter its incidence was more or less constant. Atrophy of the endometrium was noted as early as one year after the menopause, and the incidence of this pattern did not increase appreciably in later age groups.

Specimens Obtained Postmortem

The majority of the patients in whom curettings were examined were suffering from uterine or vaginal prolapse, and it might be argued that this condition is not unassociated with vascular and endocrine changes which might influence the endometrial pattern. As this would give a false impression of the normal, recourse was had to the study of postmortem material from patients dying of general medical or surgical conditions. All of these patients were at least 2 years after the menopause. None of them had any symptoms or functional disturbance relating to the genital tract. An additional advantage of this group of cases was that the entire endometrium lining the uterus was available for study. The distribution of endometrial pattern in the uteri in this series is shown in Table III.

TABLE III

Incidence of Endometrial Pattern in Intact Uteri

Type of Endometrium	Atrophic	Inactive Cystic Gland Pattern	
		Polyp	Diffuse
Percentage	65	15	20

In more than half the cases in which atrophy was noted an occasional cystic gland was present. It will be seen that the diffuse cystic gland pattern occurred in 20 per cent of the specimens compared with 3·9 per cent noted in the series where the diagnosis was made from a study of the curettings. Polypi with inactive cystic glands were found in 15 per cent of cases, a much lower incidence than was found in the curettage series. There were no examples of active hyperplasia of the endometrium in the uteri obtained at postmortem, but it should be noted that only 3 of these patients died within a period of 5 years after the menopause.

Study of these specimens gave further information in regard to the group showing diffuse cystic dilatation of the glands. In curettage specimens the impression is that this type of endometrium is bulky, but examination of the intact uteri shows this to be false. Although the cystic glands are large they form superficial bulges on an endometrium which is otherwise thin and atrophic. Nor do these glands extend in depth into the wall of the uterus.

In a consideration of the inactive types of endometrium there is an apparent lack of agreement between the incidence observed in the curettage series and in the specimens obtained at postmortem where the whole uterus was available for study. Where curettage did not result in the obtaining of endometrial tissue for examination the presence of mucus was sometimes noticed. It is probable that this is due to rupture of the cystic glands by the curette and the incidence of the diffuse cystic gland pattern noted when the entire uterus was examined, namely 20 per cent, is the correct one.

Endometrial polypi with cystic dilated glands were found in 39 per cent of curettings, but if the non-productive curettage cases are included in the assessment, then the figure falls to 5·25 per cent. These polypi are most frequently found near the fundus of the uterus as is shown by a study of intact uteri, and it is probable that in a number of cases the curette fails to locate them, or at most, scrapes the surface and draws a little mucus from the ruptured glands. The percentage noted in the series in intact uteri, 15, is likely to represent the true incidence of these senile polypi.

The high incidence of simple and cystic atrophy of the endometrium observed in this series gives support to the view already expressed that one or other of these atrophic patterns is present in most cases where curettage fails to produce endometrial tissue. It follows that the calculated incidence of activity of the endometrium (2·5 per cent) is likely to be a true over-all figure, although the incidence would be higher in the earlier post-menopausal years.

Discussion

The traditional conception of the post-menopausal endometrium is of a mucosa which has become thin and atrophic with a few, small, inactive glands set in a sparse fibrous stroma. That this was not invariably so was reported by Payne (1937) who noted post-menopausal endometrial hyperplasia in 8 patients who were not suffering from uterine bleeding. Novak and Richardson (1941) undertook a study of the post-menopausal endometrium as part of the larger subject of post-menopausal bleeding. They studied the endometrium from 137 post-menopausal women, 78 of whom were not suffering from bleeding. Of these they found atrophy in 43 per cent, a "retrogressive" cystic pattern in 32 per cent, active hyperplasia in 20 per cent and proliferation in 5 per cent. In contrast to my own findings that active hyperplasia was with one exception found in the first 5 years after the menopause, they noted this appearance in the endometrium of patients long past the menopause. This gives a higher incidence of hyperplasia than was found in the present series. However, in their communication, they took no account of cases where curettage produced no endometrium. As these probably represented atrophy of the endometrium in most cases it would seem that their figures give an erroneous impression of the actual incidence of activity of the endometrium in post-menopausal women who have not had any bleeding. Novak has given the name "retrogressive hyperplasia" to the histological pattern which I have described under the heading of "inactive cystic gland pattern". He considered that this endometrium resulted from hyperplasia occurring at the time of the menopause. I have been reluctant to use this term as it is very doubtful if the use of the word "hyperplasia" is appropriate.

Gianaroli (1947) found both simple and cystic atrophy, the latter pattern being present in a polyp in 15 per cent of cases. Telangiectasis was noted in 26 per cent of the total cases and there was frequent haemorrhage into the endometrium.

Speert (1949) examined uteri taken from 60 women whose only gynaecological abnormality was a prolapse. He found cystic glands in 72 per cent and in 16·6 per cent of cases an endometrial polyp was present. The histological description of the polypi shows them to be of the inactive cystic gland pattern, and the incidence corresponds closely with my own findings. He also

stressed the vascular pattern of the polypi and noted particularly the presence of veins just below the surface epithelium. As he was frequently unable to trace a connexion between the glands and the surface epithelium he considered the cystic glands to be retention cysts.

Foix (1952) in a study of curettings in 100 cases found the endometrium to be atrophic in 86 per cent of asymptomatic post-menopausal women, and in 80 per cent of these there was cystic change in the glands. Proliferative activity was present in 10 per cent of cases and secretory activity in 3 per cent. The relatively high incidence of secretory activity is probably to be explained by the fact that he included in his series patients within 6 months of the cessation of menstruation.

Thus, from a study of the literature and my own observations, it would appear that atrophy of the endometrium associated with a varying incidence of cystic dilated glands is present in about three-quarters of all post-menopausal women who have had no bleeding since the menopause. Endometrial polypi, composed essentially of cystic glands, are found in about 15 per cent of all cases. My own findings correspond closely with those of Speert, Gianaroli and Novak and Richardson in this respect.

There is a discrepancy between the incidence of active hyperplasia reported by the authors quoted, and indeed between the incidence noted in curettage specimens and in the study of the entire uterus. It is very unlikely that the incidence of hyperplasia is as high as that reported by Novak and Richardson and their elimination of cases of non-productive curettage from the analysis gives a wrong interpretation. When this factor was taken into account in the present study the incidence of hyperplasia and proliferation fell from 18·6 to 2·5 per cent. My own observations showed that the great majority of instances of active hyperplasia occurred within a few years of the cessation of menstruation, and it seems reasonable to conclude that the absence of hyperplasia in the postmortem material was because of the advanced age of the patients who comprised this group. It is, therefore, difficult to assess accurately the actual incidence of active hyperplasia of the endometrium in the post-menopausal woman. The true figure probably lies between the values I have given, namely, 18·6 to 2·5 per cent, the highest incidence being noted in the first 5 years after the menopause.

The Significance of Senile Endometrial Polypi

The incidence of senile endometrial polypi in asymptomatic post-menopausal women, in my series 15 per cent, is similar to that found by other authors but there appears to be considerable doubt regarding the significance of this finding. They may occur many years after a normal menopause even in the absence of bleeding. The term "polyp" is a clinical rather than a pathological one, referring simply to a growth which is attached by a pedicle, and not indicating in any way its histological characters. The endometrial polyp consists of a localized heaping up of that tissue. These polypi may be small or large enough to fill the uterine cavity. On occasion the pedicle is so long that the body of the polyp protrudes through the cervix. The polyp may correspond to the general endometrial pattern as in cases where the whole of the endometrium lining the uterus is thick and polypoidal. In the post-menopausal woman, however, the polyp is frequently solitary, composed of an inactive cystic gland pattern and always found in association with a thin inactive endometrium.

Polypi are found in the uterus of asymptomatic post-menopausal women, in cases of post-menopausal bleeding and in association with endometrial carcinoma and their presence has been subject to varied interpretation. Fletcher Shaw (1931) referred to the anomalous finding of an endometrial polyp in association with an atrophic tissue like the endometrium after the menopause. Whitehouse (1934) considered that small polypi could be explained on a mechanical basis. He did not think that the cause was necessarily hormonal but suggested that they might be due to a lowering of intra-uterine tension. Hirson (1939) considered that reparation following severe inflammatory change involved the overgrowth of glandular tissue. Fahmy (1933) regarded polypi as benign tumours, presumably of an adenomatous variety. It was inevitable that an explanation involving endocrine factors would be forthcoming. Taylor

(1932) referred to the frequent finding of polypi and endometrial hyperplasia in association, and suggested a common cause for the conditions. Novak and Richardson (1941) gave the name "retrogressive hyperplasia" to the inactive cystic gland pattern which is present in these polypi. They considered that these polypi occurred in the uterus of a patient whose terminal menstrual cycles had been anovulatory, the endometrium showing cystic glandular hyperplasia at that time. In the post-menopausal years a process of mummification takes place and the inactive cystic gland pattern develops. Thus, according to both these views, endometrial polypi with cystic dilated glands are related to endometrial hyperplasia and by inference to abnormal oestrogenic activity. In the former the hyperplasia is thought to be co-existent and in the other preceding—often by many years—the formation of endometrial polypi. Speert (1949) returned to the mechanical explanation for the development of polypi. He considered that the dilated glands represented simple retention cysts and the polypi themselves merely a localized aggregation of such cystic glands. It is difficult, however, to interpret the findings of most of these observers since they do not give a histological description of the type of polypi to which they refer.

A study of the histology of these endometrial polypi found in the present series gives a general impression of inactivity of the tissues. The epithelium lining the glands is flattened and mitotic figures are absent. The stroma is less cellular than endometrial stroma usually is and mitotic figures are absent. Indeed the resemblance to hyperplasia is entirely based on the disparity in the size of the glands, and it is noteworthy that the glands of polypi frequently attain a size much larger than is ever seen in active hyperplasia.

In order further to assess any possible relationship between endometrial polypi and hyperplasia a comparison was made of the incidence of the two conditions in the post-menopausal woman—with and without bleeding. There were 80 senile polypi of the inactive cystic gland pattern from 1,521 patients without bleeding, an incidence of 5·2 per cent. The incidence of hyperplasia in the same series was found to be 1·8 per cent. These figures represent the findings on curettage, but it seemed that the figure obtained in a study of the entire uterus, namely 15 per cent, was more likely to represent the real incidence of senile polypi. If the former figure is utilized the ratio between endometrial polypi and hyperplasia is 3 to 1 or, if the more accurate figure is accepted, the ratio becomes 8 to 1.

In 537 cases of functional post-menopausal bleeding there were 76 cases of senile polypi and 110 instances of active hyperplasia, an incidence of 14·1 and 20·5 per cent respectively. The ratio between endometrial polypi and hyperplasia is now reversed, being 2 to 3. This great diminution of the ratio of endometrial polypi to hyperplasia of the endometrium scarcely suggests that these focal aggregations of endometrium are examples of hyperplasia.

It may be, however, that these polypi represent examples of previous hyperplasia at the time of the menopause in which retrogression has occurred. If this is so, then there should be a high incidence of the abnormal menopause accompanied by excessive bleeding in women whose uterus is later found to contain a senile endometrial polyp. The average age at menopause of these patients was 47·8 years, a figure which is in close agreement with the average age in all the endometrial patterns studied. Patients in whom senile polypi occur do not have a later menopause than patients who subsequently show endometrial atrophy.

There were, in all, 156 patients in whom the finding of a senile endometrial polyp was noted. In 147 instances the menopause occurred naturally without excessive bleeding at that time. There were 3 cases where a menopausal dose of deep X-ray was given because of menopausal menorrhagia and twice radium was used for similar indications. There were 3 patients in whom the menopause followed bilateral oöphorectomy undertaken because of benign ovarian cysts or chronic salpingo-oöphoritis. Thus in only 5 cases out of 156 was there a clinical history of menopausal menorrhagia, and in only 1 of these was cystic glandular hyperplasia present. In the other instance where endometrium was available for examination a typical late secretory pattern was seen. Cystic glandular hyperplasia was also noted at curettage 2 years

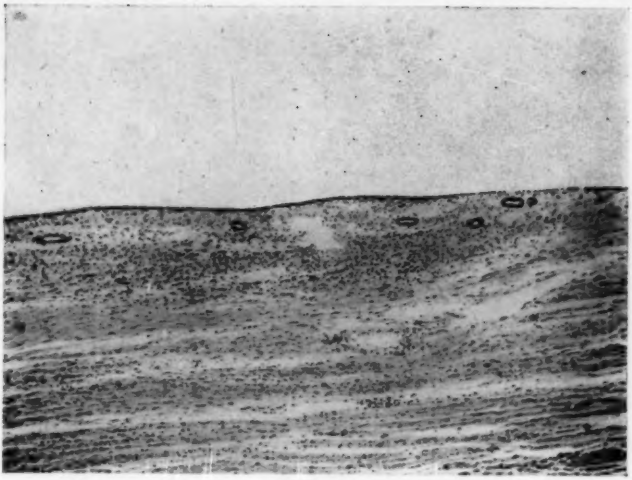

FIG. 1

Simple atrophy of the endometrium. Patient aged 59 years and 11 years after the menopause. H. & E. × 50.

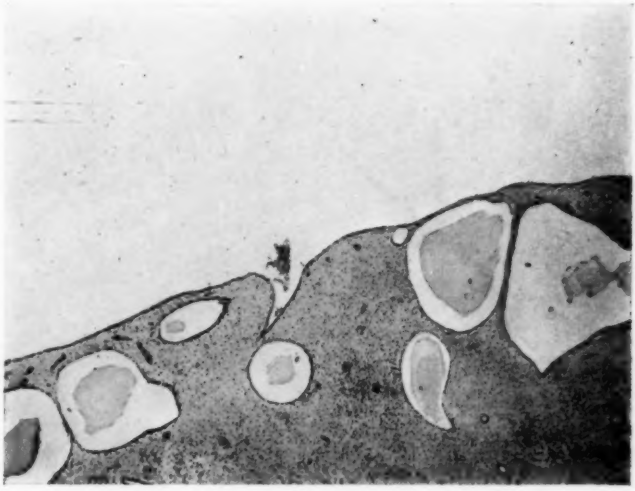

FIG. 2

Inactive cystic gland pattern. Patient aged 67 years and 20 years after the menopause. H. & E. × 50.

FIG. 3

Senile polyp of similar histological structure obtained 17 years after the menopause from patient aged 64 years. H. & E. ×5.

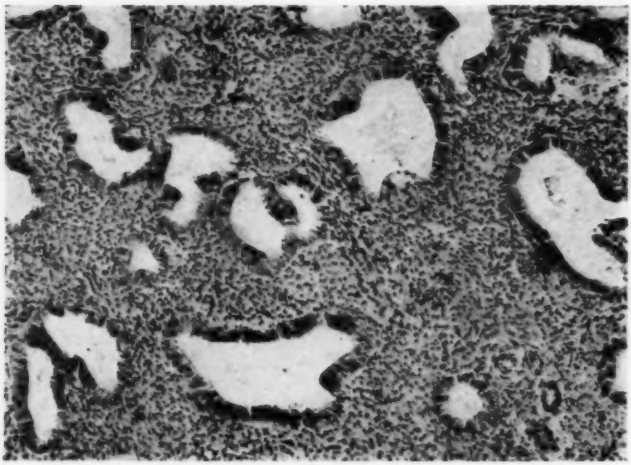

FIG. 4

Active hyperplasia of the endometrium occurring 3 years after the menopause. Patient was aged 51 years. H. & E. ×100.

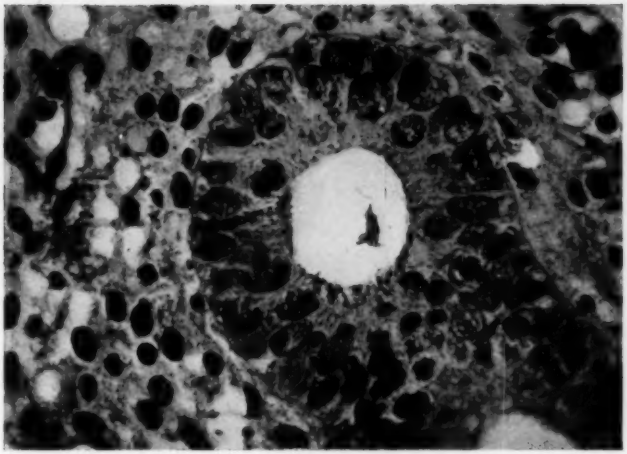

FIG. 5

Active mitosis in glandular epithelium in active hyperplasia. H. & E. × 700.

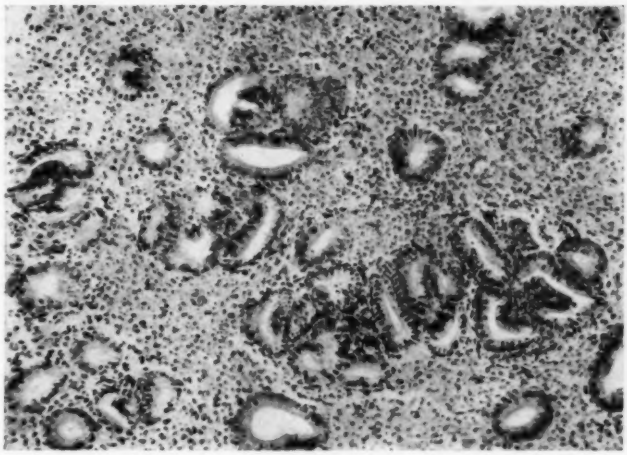

FIG. 6

Adenomatous hyperplasia of the endometrium in a patient 2 years after the menopause. H. & E. × 100.

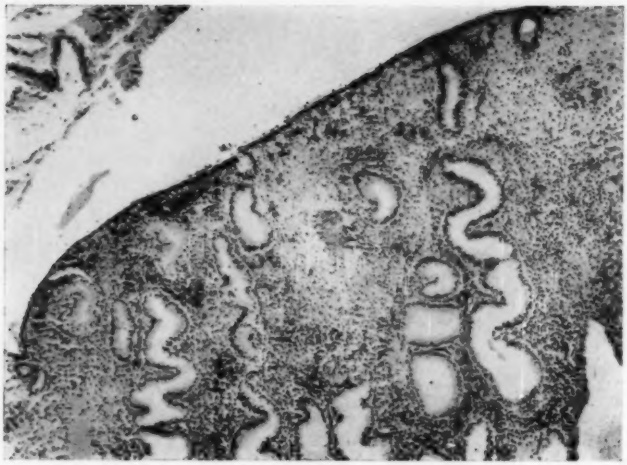

FIG. 7

Secretory endometrium obtained a year after the date of the last period in a patient aged 51 years. H. & E. ×75.

prior to the menopause in 1 instance. The periods subsequently were normal for 2 years at which time they stopped. It is therefore possible that ovulatory cycles followed the abnormal bleeding episode.

These 2 cases represent the finding of a senile endometrial polyp in the uterus of patients known to have had hyperplasia of the endometrium at or near the time of the menopause. But the fact that this sequence was noted only twice in 156 cases suggests that this is not in fact the normal mode of development of such polypi.

The inactive cystic gland pattern was found to occur diffusely throughout the endometrium in 20 per cent of asymptomatic post-menopausal women, and polyp formation of similar appearance was noted in an additional 15 per cent. If such patterns were to be considered the aftermath of hyperplasia at the time of the menopause as suggested by Novak and Richardson, the inference would be that such a condition was present in more than one third of all women of this age. This does not seem likely from a consideration of the clinical history of these patients.

I have referred to the histological appearance of inactivity in the endometrium showing a cystic gland pattern. The only difference between an atrophic endometrium and the diffuse cystic gland pattern is the presence in the latter of distended glands. These may well be simply retention cysts resulting from the occlusion of the gland openings caused by atrophy and contraction of the lining epithelium. Such an explanation is in accord with frequency of occurrence of the cystic gland pattern which would imply a cause operative in more than one-third of cases. It is also compatible with the inactive appearance of the stroma.

There is thus no evidence that endometrial polypi of the inactive cystic gland pattern are examples of active hyperplasia nor yet of "retrogressive" hyperplasia. The resemblance to hyperplasia is a superficial one, and is based on the disparity in size of glands, taking no note of the inactive histological appearance. The diffuse cystic gland pattern is probably to be regarded as a variant of atrophic endometrium and it is possible that senile polypi are local aggregations of endometrium of similar cystic gland structure.

Summary

A study was made of the results of curettage in 1,521 post-menopausal patients who had not suffered from bleeding since the cessation of menstruation, and the histological findings described. Simple atrophy was found in 31·5 per cent of the 206 cases where endometrium was obtained for microscopic examination. The incidence of active hyperplasia was 12·6 per cent, but reasons were adduced for the belief that this figure was artificially high. The majority of such cases occurred in the early post-menopausal years. An inactive cystic gland pattern was noted in 42·7 per cent of cases; in the majority of cases it was in polyp formation. The investigation of uteri obtained at post-mortem confirmed that this gland pattern was of common occurrence and suggested a mechanical explanation for the development. Histological and clinical findings did not provide any evidence that this gland pattern was related to endometrial hyperplasia or to excessive oestrogenic activity. The fact that active hyperplasia and endometrial polypi of cystic gland pattern occur in women past the menopause who have not suffered from bleeding must be taken into consideration in the interpretation of the endometrial pattern encountered in cases of post-menopausal bleeding and in association with endometrial carcinoma.

Acknowledgments

I would like to express my thanks to Doctors McIntyre, Hewitt and Clement for permission to study case records from their files, and to Dr. Govan for his advice and help in the preparation of this paper. I would also like to thank Mr. Pearston for his work in producing the photomicrographs.

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ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

A MEETING of Council was held at the College House on Saturday, 25th September, 1954, with the President, Mr. Arthur A. Gemmell, in the Chair.

The following were admitted to Fellowship:

Sir Stanford Cade.
Mr. Christiaan Frederik Krige.
Miss Eileen Mary Whapham.

The following were admitted to Membership:

George Jerzy Arendt.
Antony Livio Baccarini.
Karl George Ball.
Archibald Walker Banks.
John Maurice Barrett.
Antony Edward Robin Buckle.
Donald Everett Burgess.
John Duncan Bury.
Elizabeth Blanche Butler.
Desmond John Cassidy.
Keith Wallace Cochrane.
John Victor Malcolm Coppleson.
John Crossley.
Peter Harry Crowe.
Gordon Theodore Martineau Cummins.
Ben Danzig.
Sheila Paterson Davidson.
Desmond James Dooley.
Mary Muriel Essex-Lopresti.
Reginald Arthur William Feakes.
James Patrick Beaumont Fitzgerald.
Chonira Belliappa Gangamma.
Robert Graham Gudex.
Muriel Sheila Hill.
Malcolm Hindmarsh Jameson.
Edwards William Jeyaratnam.
Donald Keith.
Barry Lee Griffiths Kneale.
Marjorie Amy Clara Kuck.
William Lees.
George Alfred Lewis.
Geoffrey Douglas Roland Lilburne.
William Peter McLaughlin.
Malcolm Campbell Macnaughton.
Joan Marshall.
Paul Wanostrocht Mitchell.
Marjorie Christine Bremner Moore.
Hugh O'Hara.
Donald Leslie Phillips.
Harry Maree Pretorius.
William Leslie Gray Quinlivan.
John Roper.
Leon Rubin.
Bernard Maurice Sandler.
Supriya Sen Gupta.
Kusum Kumari Sharma.
Pamela Mary Smith.
Derek Tacchi.
James Gavin Amess Troup.
Jeffery Walsh.
Joseph Noel Ward.
Herbert William Wilson.

REPORTS OF SOCIETIES

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

April 1954

A Meeting of the North of England Obstetrical and Gynaecological Society was held at the General Infirmary, Leeds, on Friday, 23rd April, 1954. The President, Dr. K. V. Bailey, was in the Chair.

Dr. F. Da Cunha described

Two Uncommon Flying Squad Emergencies

Case 1. Acute inversion of the uterus

A multiparous woman, 25 years old had had her 2 previous babies in hospital, but after both there had been a retained placenta and post-partum haemorrhage.

In this third confinement, at home, the placenta was again retained. Following over-zealous attempts by the midwife to express the placenta, the uterus became completely inverted and the patient gravely shocked. When he saw her, she appeared moribund; she was grey and pulseless, and her blood pressure could not be recorded. The uterus was visible between the thighs, completely inverted, with the placenta attached to the fundus.

Blood transfusion was immediately started, one pint of non-cross-matched Rh negative Group O blood being given under pressure, in about 5 minutes; a second pint was allowed to run in more slowly. The patient's pulse was now faintly perceptible, but the blood pressure still could not be recorded.

Without delay, under general anaesthesia the inverted mass was examined, and the placenta stripped off the fundus; the mass was then gently replaced within the vagina, and by gentle taxis the uterus was returned within the abdomen quite easily. Simultaneously, there was a marked improvement in the patient's condition. Transfusion of a third pint of blood was continued, and one hour after replacement of the uterus the blood pressure was 120/60. The patient recovered completely.

Comment. Dr. Da Cunha remarked that it might be thought that the last word had been said on this subject, for the literature dealt very fully with it. However, while it would be unjustifiable to draw hard and fast conclusions from a single case, analysis of the literature and the standard texts showed difference of opinion with regard to treatment in the presence of shock. Briefly, where shock was present (and often profound), should treatment be limited to resuscitation only, until the patient's condition improved sufficiently to allow replacement of the inversion? Or, resuscitative measures having been commenced, should immediate replacement be attempted in the presence of shock, before this became—as it might—irreversible? An analysis of reported cases showed that, where replacement was delayed until recovery from shock occurred, recovery did *not* ensue and, whether ultimate replacement of the uterus was successful or not, the patient died. In this case, as in others, resuscitative measures were not followed by a noticeable improvement in the patient's condition: but replacement of the uterus without further delay resulted in recovery.

Dr. Da Cunha added that there was still a place for reduction by taxis, if this were carried out before oedema or a contraction ring prevented the return of the inversion; in the latter eventualities O'Sullivan's hydrostatic method would appear to be more advantageous and to have been attended by many successes.

Discussion. Dr. Dewhurst discussed the difficulty of diagnosis when inversion was incomplete. If the shock did not respond to blood transfusion, the inversion should be reduced without delay.

Miss Mills described a case in which shock developed after the replacement of the inversion, the patient dying 12 hours later.

Drs. D. C. A. Bevis, Barkla and Macfarlane and Mr. D. W. Currie also described cases they had seen, and the general opinion was that immediate correction of the inversion was indicated.

Case 2. Amniotic embolism

A primigravida, aged 32, had her labour induced by drug induction when she was 10 days overdue. Six hours after the onset of labour, the membranes were noted as ruptured. One hour later she suddenly collapsed. When he saw her 20 minutes later she was very ill, intensely cyanosed and dyspnoeic; she died within a matter of minutes, while oxygen was being administered.

There was no evidence of bleeding nor of any abdominal catastrophe, either at the time or on post-mortem. The head was engaged and the cervix fully dilated. The only significant finding was histological; sections of the lung showed blockage of branches of the pulmonary artery in one lung by amniotic fluid and epithelial squames. There was also emphysema and pulmonary oedema. The amniotic emboli were also to be seen within the uterine sinuses. In the absence of any other finding the presumptive cause of death was amniotic embolism.

Comment. Many cases of this condition had been reported, mainly in America, since 1941, and a well illustrated case by Shotton and Taylor in this country in 1949, showing emboli in the lungs, uterine sinuses, brain, and coronary vessels. There has also been a critical paper by Tunis analyzing 25 of the American cases, and suggesting that in all of them there was some other overlooked explanation of collapse and death and that amniotic embolism did not occur, or was only an incidental finding. He would therefore be interested to know whether any member had seen a similar case, or had any views on the question of treatment.

Discussion. Prof. A. M. Claye said that if there were

doubt whether amniotic emboli caused death, should not the pathologist take sections from the lungs in all maternal deaths to see whether such debris were found otherwise?

Mr. D. W. Currie had seen 2 deaths from amniotic embolism, the diagnosis being accepted by the coroner and Miss Patterson showed slides of the sections of the lungs of these patients.

Dr. D. C. A. Bevis described a case of

A Double Monster

Case History

The patient, aged 23, first attended the antenatal clinic at the 30th week of her first pregnancy, when referred for booking as a twin pregnancy had been diagnosed. She had a strong family history of twins; she had a twin sister and both her father and mother had twin siblings. The pregnancy was uneventful and the first foetus presented by the vertex and remained so throughout the pregnancy but the lie of the 2nd twin was always in doubt. She was admitted at the 39th week for rest but, as her blood pressure rose to 140/110, labour was induced by artificial rupture of the membranes. Contractions began 3 hours later and the labour appeared to be quite normal. After 19 hours the cervix was fully dilated and 15 minutes later the head of the first twin was visible. Half an hour later the head was crowning but, in spite of active cooperation from the patient, there was no further advance. The registrar performed an episiotomy and delivered the head with Wrigley's forceps. Again there was no advance and it was at this stage that he himself saw the patient for the first time.

On examination the hand of the 2nd twin was found to be prolapsed behind the delivered head and the 2nd twin appeared to be lying transversely with its head to the right. The patient was rapidly anaesthetized and intra-uterine examination showed the twins to be joined together by the thorax with the head of the 2nd twin bent backwards against its own spine. At this stage the twins were still alive and he wondered whether they could have been delivered without damage to themselves or the mother.

It was impossible to slide or rotate one child on the other and deliver the first baby as far as the bridge, and brute force, if not complete ignorance, had already been tried. He therefore took the patient to the theatre and communed with himself how to get the delivered head back through the vagina. This problem solved itself, however, as by the time the theatre was ready the foetus was dead; decapitation was carried out followed by an uneventful lower segment Caesarean section. The twins were female, joined at the thorax and upper abdomen as far as the umbilicus and together weighed 20 pounds. The placenta weighed 2½ pounds and was uniovular. The patient had a low grade pyrexia for a few days which responded to chloromycetin and she was discharged well on the 17th day.

Comment. The subject of conjoined twins, said Dr. Bevis, had been admirably reviewed by Aird in *The British Medical Journal* of 10th April, 1954, but naturally with little reference to the obstetric problems. Too few cases have been reported to draw many definite conclusions. The diagnosis could be made with a fair degree of certainty antenatally by X-rays. Indeed the radiologist who saw the film in this case did query the diagnosis and requested repeated pictures, but his request was overlooked. The diagnosis could be clinched by repeated X-rays in labour when the relative positions of the foetuses would not change as labour progressed. There was no doubt that abdominal delivery should then be undertaken in the interests of both mother and babies but he wondered whether there was any way these particular twins could have been delivered vaginally with any degree of safety.

In fact these particular babies could not have been salvaged as the 2nd twin had a grossly deformed head, probably as a result of pressure inside the uterus, it being squashed asymetrically and hyperextended on the trunk. The bridge contains a common liver (which probably could have been separated) but there was a common heart with two auricles, one ventricle and two aortas. All other organs appeared to be separate.

His main object in bringing the case before the Society, concluded Dr. Bevis, was to enquire its views on artful obstetrics in relation to these cases.

Discussion. Mr. F. Stabler pointed out that foetal deformities due to pressure corrected themselves postnatally and therefore hope for the survival of the second twin need not have been abandoned.

Miss K. Liebert, Mr. C. E. B. Rickards and Mr. D. W. Currie all described cases they had seen, in the last the membranes being ruptured artificially early on and delivery being effected without difficulty.

Dr. J. B. Cochrane described

A Case of Fibroma of the Vulva

Dr. Cochrane said he was reporting this case because substantially large labial fibromata were not very common, and secondly it illustrated the remarkable forbearance frequently shown by women in the presence of an extremely incommoding situation.

Case History

The patient, aged 36, had first noticed an abnormal swelling on her right labium majus 20 years previously. The swelling gradually increased in size until about 1 year ago, when the enlargement became more rapid. Two months before her first visit to him in January, 1954, it had begun to ulcerate at its base and the consequent discharge soiled her clothes. Also about this time she noticed another small swelling on her right buttock. Fearing an epidemic of such tumours, she decided to seek advice on the matter and was referred to him by her own doctor, who apparently had been aware of the labial tumour for the past 8 years.

Examination showed a large pedunculated pear-shaped tumour arising by a pedicle some 8 inches long from the right labium majus and with extensive ulceration at its base. A small cystic tumour, presumed to be a lipoma, was also present on the right buttock. No other

abnormalities were found and so she was duly admitted to hospital and both lumps were removed without difficulty. Section of the labial mass showed it to be an oedematous and infected fibroma with simple ulceration at its base and no evidence of malignancy. The buttock tumour was, as thought, a simple lipoma.

After operation, when the patient realized how simple her redemption had been, she vouchsafed the information that at the births of each of her 3 children, ages 13, 8 and 5, perineal suture had been necessary each time and she had been advised on all occasions to have the labial mass removed but had felt so ashamed and self-conscious of her genital disfigurement that she had not the courage to do so.

Discussion. The President wondered how the obstetrician at her confinement had resisted the temptation to remove the fibroma.

Mr. F. Stabler recounted the case of a fibroma in a university lecturer who thought she had grown a male organ, and broke off her engagement. He also described two cases of soft fibromata which extended into the iliac fossa and through the sciatic foramen.

Dr. R. E. Rewell described a case of

ACUTE PELVIC TUBERCULOSIS COMPLICATING PREGNANCY

Case History

A primigravida aged 25 was delivered normally at 34 weeks of a normal female child weighing 3 pounds 11 ounces at the Liverpool Maternity Hospital on 13th July, 1953, following a small accidental haemorrhage. The placenta showed an "infarct" and a retroplacental clot of about 3 ounces was present.

On the fifth day of the puerperium she started a pyrexia, which on that day reached 101·4° F. and thereafter continued remittently, reaching 104° F. on occasion. At first she was very well and was annoyed at not being allowed home. Aerobic and anaerobic cultures of lochia, blood and stool cultures, and blood agglutination against the enteric and brucella types of organisms all gave negative results. The blood count was normal and so was an X-ray of the chest. The urine was sterile. Finally, signs of the presence of fluid in the abdomen became evident and on the 22nd day of the puerperium (4th August, 1953) laparotomy was performed which revealed an acute pelvic peritonitis, evidently tuberculous. The fluid swarmed with acid-alcohol-fast bacilli and yielded a heavy growth of *Mycobacterium tuberculosis* of the human type, sensitive to streptomycin. Both tubes were dilated and the left one was removed. The wound continued to discharge.

Despite the exhibition of streptomycin and isoniazide in full doses she went slowly downhill. On 7th October, 1953 she became drowsy, unreceptive and incontinent with neck rigidity. The C.S.F. showed changes typical of tuberculous meningitis and acid-alcohol-fast bacilli were found in it. She died on 9th October, i.e., 12 weeks after delivery.

Findings at Necropsy. This was performed on the day of death. The body was very wasted. The cardiovascular and endocrine systems were normal. There was extensive miliary tuberculosis throughout both lungs and this was nowhere confluent. The peritoneal cavity was largely obliterated by dense adhesions enclosing pockets of caseous pus, which filled the pelvis. The liver showed advanced fatty change, but the other abdominal viscera were normal. The remaining tube and the cavity of the uterus contained caseous pus. The kidneys showed fatty change. Within the skull the C.S.F. was under pressure but clear, while gelatinous exudate covered the base of the brain. No gross tubercles were seen. Death was attributed to miliary tuberculosis with terminal tuberculous meningitis.

Histology. The placenta was received in formol-saline and so was unsuitable for culture. It did not appear abnormal and as the unusual interest of the case had not then become apparent, only one block was taken for section. It showed only the usual areas of necrosis of the trophoblast seen late in pregnancy, the villi appearing normal. Later a prolonged search for acid-fast bacilli in specially stained sections proved fruitless.

The lungs and brain showed typical miliary tuberculosis and tuberculous meningitis respectively. Both oviducts, the one removed at operation and that left in the body until death appeared, on gross section, to be lined with gelatinous, fibrinous exudate and somewhat distended. Microscopically there was complete replacement of the mucosa and submucosa by what appeared to be acute, non-specific granulation tissue, consisting of polymorphs, fibrin and plasma cells and showing none of the features classically associated with tuberculosis. Groups of inflammatory cells lay between the muscle bundles of the wall. A few acid-fast bacilli were found in the exudate.

Fate of the baby. The only contact of the baby with her mother after delivery was lying in a cot on the other side of the same room for a few days. She was soon removed to a nursery and, although never requiring the full regime for markedly premature babies, was fed artificially, but not from her mother's milk. She was removed to the Royal Liverpool Children's Hospital when aged 11 weeks and before her mother's death. An extensive, tuberculous bronchopneumonia was then found to be present which was treated with streptomycin and isoniazide. The child made a complete recovery. The organism was not isolated.

Discussion. The question was whether the acute pelvic tuberculous infection was present during the pregnancy. It seemed likely from the degree of change which had taken place by the time of the laparotomy, but the negative findings in the placenta and the slight delay in the onset of the pyrexia were against it. The development in the baby of an acute tuberculous condition supported the idea of the infection being present before delivery. There was no obvious primary disease outside the pelvis and no suggestion could be made as to the source of infection.

The absence of any specific features in the lesions of the tubes was at first sight surprising. But it was to be expected when the infection was hyperacute and especially when tissue resistance was lacking or had broken down completely. Thus, most cases of tuberculous meningitis showed no specific features in the exudate, neither were

such present in the meninges of this woman, either macroscopically or microscopically. A similar appearance was seen commonly in tuberculous bronchopneumonia spreading rapidly following a breakdown of tissue resistance. This was most obvious in the tissues of animals which had had no chance to develop resistance. He had observed this frequently in wild-caught animals brought into captivity, e.g., in many monkeys and small carnivores, in certain marsupials and even in so large a cat as the cheetah (*Acinonyx jubatus*).

The presence of acid-fast bacilli in sections of the tubes was also noteworthy. They were extremely scanty in well-developed tuberculous granulation tissue showing specific features, but were common in the really acute type, in all mammals. In birds and reptiles huge masses of acid-fast bacilli might lie in the tissues surrounding chronic caseous lesions. However, such animals seldom showed what in mammals would be regarded as the specific picture. Even in chronic processes epithelioid and giant cells were usually absent and the lesion consisted of a caseous core surrounded by developing fibrous tissue with a heavy infiltration of round cells. But in such animals polymorphs were few in the blood and might not be strictly homologous with those of mammals.

In conclusion Dr. Rewell thanked Mr. P. Malpas, who cared for the mother and Dr. H. G. Farquhar, who looked after the baby, for permission to publish this report.

Discussion. Some members had seen similar cases. Mr. G. Winchester had noted while performing a Caesarean section some free fluid and bruising of the peritoneum in a patient who during the puerperium developed a tuberculous tubo-ovarian abscess. He had also seen an ectopic pregnancy in a tuberculous tube. Miss E. M. Mills described the case of a woman who was found to have a tuberculous tubo-ovarian abscess 2½ weeks after a normal delivery. Dr. A. A. Smith had had to perform a Caesarean section in a case in which the head could not engage because of large tuberculous glands in the pelvis.

With regard to Dr. Rewell's case, Dr. J. W. A. Hunter thought it likely that the tuberculosis was contracted late in pregnancy, and Mr. G. W. Theobald speculated whether a "clean sweep" operation at an early stage might have saved the patient's life.

Mr. P. Malpas described a case of

Abdominal Wall Reaction, with Omental Secondaries

A woman aged 57 had generalized peritoneal carcinomatosis probably secondary to a symptomless carcinoma of the sigmoid. The histological appearances were those of a mucus-secreting adenocarcinoma. The great omentum, infiltrated by growth, was adherent to the posterior aspect of the anterior abdominal wall in the midline above the pubes over an area roughly the size of the palm of the hand.

The patient complained of loss of weight and anorexia, and in addition said that for the past month she had found it difficult to straighten herself after stooping. She had to be helped up into a sitting position after lying on the examination couch. The one positive finding abdominally was an ill-defined swelling above the pubes. It was impossible to say whether or not this swelling, which laparotomy later disclosed as omental metastases, was situated within the abdominal wall.

The abdomen was opened by a transverse suprapubic incision. The rectus sheath and the oblique aponeuroses were normal. They were incised along the line of the skin incision and dissected upwards to expose the recti muscles. The inner margins of the muscles were seen to be separated by an interval some 2½ inches wide. The muscles themselves were replaced by a thin shining tendinous aponeurosis for a distance of about 3 inches above the pubes. Above this level the muscle appeared to be normal. In other words the muscles had not only become separated but had atrophied. The omental malignant plaque was adherent to the peritoneum of the anterior abdominal wall over an area corresponding closely to the combined area of separation and atrophy of the recti muscles. There was no herniation of the peritoneum.

The divarication of the recti therefore was not due to any protruding tumour or peritoneal sac, and the atrophy must have taken place in the course of at the most 2 months.

Atrophy of voluntary muscle in the vicinity of a malignant tumour was a recognized phenomenon. The disappearance of the fibres was preceded by degenerative changes. Whether the change was solely due to pressure or whether neurotrophic factors were responsible was difficult to say. In a recent case of a large hydronephrosis complicating a 30-weeks gestation, the abdomen was so distended that initially acute hydramnios was diagnosed. The patient was critically ill and because of this the membranes were ruptured artificially, and it then became apparent that the tumour was extra-uterine. The thinning of the abdominal muscles was extreme and, were it not for the history, a diagnosis of a ruptured uterus could have been made when the liquor had escaped, so easily were the foetal parts to be felt. The muscles recovered very quickly after the nephrectomy. Such a case, said Mr. Malpas, would support the pressure theory.

FIRST VENEZUELAN CONGRESS OF OBSTETRICS AND GYNAECOLOGY

11TH TO 16TH JANUARY, 1955

at the Medical College of the Federal District of Caracas

Honorary President, Professor Pedro Gutiérrez Alfaro
Minister of Health and Social Assistance

President, Dr. Julio Calcaño — *Secretary*, Dr. J. R. Pittaluga C.

THE Society of Obstetrics and Gynaecology of Venezuela has managed to arrange the First Venezuelan Congress of Obstetrics and Gynaecology in Caracas, from the 11th to the 16th January, 1955, under the auspices of the Ministry of Health and Social Assistance of this Country.

This event has been organized in such a way that it may have the greatest scientific interest for our speciality, since two main subjects will be under review, one on Obstetrics: "Maternal Mortality", and the other on Gynaecology: "Surgery of Genital Prolapse", each of which will be discussed by four eminent specialists chosen for the purpose.

Then 15 lectures will be given of 30 minutes each on selected subjects of particular importance and topical interest, by a group of teachers of international repute, who have been specially invited.

There will also be included within the scientific programme, open discussions, clinical demonstrations, films and other aspects of scientific importance in both specialities.

Colegio de Medicos del Distrito Federal,
Plaza de Bellas Artes,
Los Chaguaramos, Caracas.

JULIO CALCAOÑ, *President.*
J. R. PITTALUGA, *Secretary.*

PROGRAMME

Subject: "MATERNAL MORTALITY"

Speakers: Drs. M. A. Sánchez Carvajal, Venezuela, J. M. Aurrecoechea, Venezuela, and J. I. Torres, Venezuela.

Discussion by: Drs. Manuel Luis Pérez, Argentina, J. Ramírez Olivella, Cuba, S. Dexeus Font, Spain, and Darío Curiel, Venezuela.

Subject: "SURGERY OF GENITAL PROLAPSE"

Speakers: Drs. A. Domínguez Gallegos, Venezuela, and Delfín Mendoza Blanco, Venezuela.

Discussion by: Drs. Tassilo Antoine, Austria, Arnaldo de Moraes, Brazil, Raul Palmer, France, and R. Baquero González, Venezuela.

Lectures

"Functional Uterine Haemorrhage", by Dr. J. C. Ahumada, Argentina.

"Clinical and Radiological Pelvimetry", by Dr. O. Rodrígues Lima, Brazil.

"General Syndrome of Adaptation in Obstetrics and Gynaecology", by Dr. J. Botella Llusiá, Spain.

"Endometriosis", by Dr. R. W. TeLinde, Baltimore, U.S.A.

"Cause, Morbid Anatomy and Management of Displacement of the Placenta", by Dr. Duncan E. Reid, Boston, U.S.A.

"Cause and Therapeutic Management of the Toxaemias of Pregnancy", by Dr. Wm. J. Dieckmann, Chicago, U.S.A.

"Organization and Function of a Maternity Hospital", by Dr. Malcolm MacEchern, Chicago, U.S.A.

"Surgery of Female Sterility", by Dr. Bernard Weinstein, N. Orleans, U.S.A.

"Obstetric Analgesia and Anaesthesia", by Dr. John Adriani, New Orleans, U.S.A.

"Genital Fistulae of Obstetric Origin", by Dr. J. Chassar Moir, Oxford, England.

"Organization and Aims of Antenatal Care", by Dr. Dugald Baird, Aberdeen, Scotland.

"Uterine Cancer in Pregnancy", by Dr. Conrado Zuckermann, México.

"Lines of Therapy in Uterine Dysfunction", by Dr. Hermógenes Alvarez, Uruguay.

"Tuberculosis in Pregnancy", by Dr. José I. Baldó, Venezuela.

"Consequences of Difficult Labour in Early Infancy", by Dr. Pastor Oropeza, Venezuela.

Free Subjects

Short papers of about fifteen minutes will be read by their authors, and should be received at the Secretariat of the Congress by the 15th November, 1954. Details of subjects and authors will be given in a subsequent programme.

BOOK REVIEWS

"Twenty-five Years: The Story of the Royal College of Obstetricians and Gynaecologists 1929-1954." By Sir William Fletcher Shaw, M.D., F.R.C.P., F.R.C.O.G., Hon. LL.D. Pp. viii + 192. Illustrated with 12 plates. London, J. & A. Churchill Ltd. Price 21s. net.

As we get older our birthdays come racing round upon us with such rapidity that we become increasingly reluctant to give them more than the merest nod of recognition in passing. But with a College—and a Royal College to boot—it is a different matter, and a Silver Jubilee rightly calls for a celebration with some pomp and ceremony.

It was this sense of occasion that prompted the President to ask Sir William Fletcher Shaw to write about the origin, early years and rise to maturity of the College. No other man could have undertaken the project with equal promise and authority, for he alone has the requisite intimate knowledge of the birth and early development of an organization of which he was in a very real sense one of the parents.

Yet he tells us that even he blenched when he got to grips with his task and saw the mass of papers to be digested, and he was glad to enlist the expert help of Dr. Harvey Flack and his associate Miss Joyce Ward. That between them, working against time as the anniversary rapidly approached, they should have produced a book, which, except in the first few pages, shows no obvious signs of hasty compilation, is indeed a matter for sincere congratulation.

To trace the origin of the idea that a College of Obstetricians and Gynaecologists was needed is something that demands more than the brief prologue allotted to it in this book. The urge towards formal incorporation in order to protect and foster their special interests—whether matters of privilege or matters of training and standards of education—is a natural stage in the evolution of the major divisions of any profession. In the case of Obstetrics—ever the Cinderella of the medical sisterhood—the smouldering embers of "sisterly animosity" were never so effectively banked down in the older metropolitan Colleges as to make this evolutionary stage either improbable or, indeed, avoidable. But what Fletcher Shaw stresses as the immediate background to our College's origin was the handicap under which the young man, desirous of specializing in Obstetrics and Gynaecology, laboured as compared with the would-be physician or the budding surgeon, owing to the lack of any recognized portal to consultant rank comparable to the existing Colleges of Physicians and Surgeons in London, Edinburgh or Dublin. The aspiring Obstetrician and Gynaecologist had therefore to spend considerable time, money and energy in fitting himself by special study of Medicine or Surgery to pass through these portals in addition to studying the special subjects of his choice.

Obviously, also, a College of Obstetricians and Gynaecologists could, and would, set up and maintain standards of training and examination which would have the effect of raising the level of professional competence and ultimately improve the status of the combined specialty *vis à vis* Medicine and Surgery. To most of those who had already reached consultant standing this close association of Gynaecology with Obstetrics was a powerful argument in favour of the proposed new College, as they were convinced that it was not in the best interests of women that the subject should become just a branch of Surgery.

How necessary all this was fifty years ago, and how abundantly the College has fulfilled the highest hopes of its founders, will never be fully appreciated by the young men and women now passing through the portal of our College to enter a specialty under conditions which that same College has been largely instrumental in transforming; but a perusal of this volume, and of the College's other Silver Jubilee book, the *Historical Review of British Obstetrics and Gynaecology 1800-1950*, will go far to reveal to them the richness of their professional heritage in the College.

Once past its rather halting first steps Fletcher Shaw's narrative moves increasingly smoothly and well. The story of how he was led to confide his own dream of a College to William Blair Bell is fascinating, especially to those who were early members of the Gynaecological Visiting Society and so were close to both men. To Blair Bell's many-sided genius and his ardent spirit Shaw does full justice and proper homage—the "restless, lovable torch-bearer", as Lord Dawson of Penn described him, "who never forgot or allowed anybody else to forget that he was bearing a torch". It is crystal-clear that, but for the happy conjunction of these two men, with their widely differing but complementary qualities of mind and character, the birth of the College would have been delayed indefinitely. And it is equally clear that the project was enormously helped by being conceived, as it were, within the circle of the G.V.S. in whose limited numbers so many of the leading Obstetrical and Gynaecological teachers of that day were to be found—Comyns Berkeley, Russell Andrews, Ewen Maclean, Munro Kerr, C. G. Lowry, to name only a few.

The complicated steps of the stately cotillion that preceded the actual recognition of the College, and in which the Royal Colleges of Physicians and Surgeons, the Ministry of Health, the Board of Trade and the acting promoters of the new College all took part, are recorded with admirable impartiality; and in the course of his record the author has introduced a number of brief little character-sketches of the principal participators, which will delight all his readers who are old enough to remember them.

When success ultimately crowned five years of effort and frustration, Blair Bell was the obvious first President,

and his three years of office were necessarily full of vital importance to the new venture. It is beyond question that without the very special characteristics of his services to the College in the formative days of its infancy, its subsequent progress could never have been the triumph which this book signalizes. "B.B." had a genius for ceremonial and ritual, and for the new College he lovingly devised and established the manner of all its necessary formalities—the opening and closing formulae of its meetings, the solemn declaration on admission as a Fellow, the gowns and mace and all the other outward trappings of the greatness with which his ever-forward-looking imagination endowed it. And such were the intensity and sincerity of his belief in the importance of these symbols that all subsequent officials have instinctively sensed their absolute rightness and have conserved them with meticulous care. Indeed they are now acquiring something of the patina of tradition.

Among the high lights of Blair Bell's Presidentship were the entry of the College into consultative relations with the Government through the Ministry of Health—a clear indication that the young College had "arrived"; his own gift of 58 Queen Anne Street, as the College House, and the opening of the new House by Their Royal Highnesses the Duke and Duchess of York.

One of the prime objects of the College's foundation was the building of a portal which would become the recognized entry to specialist status and consulting rank in Obstetrics and Gynaecology. This has now been completely achieved, but only after years of prospecting and testing for the best methods of training and examination, with the emphasis always helpfully on the former. Very properly the whole story of this line of the College's development has been brought together in one chapter, while another covers the linking up of the Dominions by the establishment of advisory Regional Committees, now mostly promoted to the status of Councils, in Canada, Australia, New Zealand, South Africa and India.

In the latter half of the book the story naturally divides itself into the periods of office of the successive Presidents —a series of six men and one woman, as different from each other as could well be imagined, but each with his and her own distinguished contribution to make. One closes the book with the feeling that the College has been singularly fortunate in its choice of Presidents, and that the quite unforeseen and unparalleled rapidity with which it has reached its maturity and present eminence has been due in no small measure to the sage leadership and drive which they and their Councillors have imparted to it.

Not less fortunate has it been in its first historian!

R. W. Johnstone

"A Textbook of Gynaecology." By K. M. MASANI, M.D.(Lond.), F.R.C.S.(Eng.), F.I.C.S. Pp. xvi + 639. With 261 figures. Popular Book Depot, Bombay, 1954. Price Rs. 17/8.

DR. MASANI has drawn on his long experience as a clinical teacher in writing this new textbook which is intended to meet the needs of undergraduates and postgraduates as well as to provide a reference book for practitioners. It is doubtful whether all these objects can be achieved in one book, especially of this moderate size, and the penalty may be a certain unevenness of character and depth. References, for example, may not be necessary in a students' textbook but they are desirable for postgraduates especially if, as here, names and methods are freely quoted.

The arrangement of the book follows traditional pattern from the initial pure and applied anatomy to the final section on gynaecological operations, and the author is to be congratulated on incorporating into his text some very recently published work. The section on malignant growths by Dr. E. J. Borges is excellent and includes a chapter on cancer of the cervix which is really at postgraduate level. There is also a useful contribution by Dr. N. S. Vahia on psychosexual disturbances. Throughout the book, clinical aspects are emphasized and diagnostic aids are placed in proper perspective.

The occidental reader might hope that the next edition will show revision of the English, which in places is far from impeccable, and correction of misspellings of names, such as Ferris for Farris and Krogger for Kroger. On the other hand he cannot fail to be intrigued by the differences in gynaecology between India and western countries which Dr. Masani emphasizes. This is particularly true in relation to endometriosis which is relatively uncommon in India. It has been suggested that this condition is due to continuous hyper-oestrinism resulting from the menstrual cycle being uninterrupted by pregnancy because of late marriage or contraception or both. It is therefore interesting to learn that endometriosis is uncommon among Hindus and Mohammedans who marry at an early age, but relatively common in the Parsi community who marry late.

"A Synopsis of Obstetrics and Gynaecology." By ALECK W. BOURNE, M.A., M.B., B.Ch., F.R.C.S., F.R.C.O.G. Eleventh Revised Edition. Pp. 536, illustrations 170. John Wright & Sons Ltd., Bristol, 1954. Price 25*s*.

THE demand for this book and the experience of its author is obvious. This is the eleventh edition and all from the same pen. Although intended mainly as a ready reference and review of accepted practical teaching, the synopsized form has allowed a much more thorough discussion than is given in many of the more orthodox texts. The reader accustomed to practise only in larger British centres might consider that the advice given in some sections is over elaborate and extensive, e.g., those on venereal disease and puerperal infection. But it must be remembered that these excellent sections will have a great use in other countries and centres where such conditions are common. The same comment applies to sections dealing with destructive operations on the foetus in neglected labours with malpresentation and gross disproportion. The sections on twin pregnancy and delivery, and breech delivery, could however, with advantage be expanded to include more practical detail. The author claims correctly that he has included only such new work as is likely to take its place as permanent new knowledge. The reader must, therefore, accept that in certain sections, where treatment fashions are changing rapidly, the advice given will be out of date, e.g. anuria

and megaloblastic anaemia. It seems a pity, however, that hyperemesis is still subdivided into neurotic and toxic varieties.

The part of the book devoted to gynaecology is excellent and covers the subject extremely well. It is difficult to pick out the best sections, as all are very good, but those on carcinoma of the cervix and uterine and vaginal wall prolapse deserve special mention.

This synopsis, thorough in its text, reliable in its teaching, with simple but telling illustrations, will prove extremely valuable to all students of the subject before and after qualification, and to junior teachers, as a source of rapid information or of revision.

"Textbook of Operative Gynaecology." By Wilfred Shaw, M.A., M.D., F.R.C.S., F.R.C.O.G. Pp. ix + 444. With 383 figures, some in colour. E. and S. Livingstone, Edinburgh and London, 1954. Price £5.

THE death of Wilfred Shaw in December, 1953, removed from the contemporary scene one who was outstanding among British obstetricians and gynaecologists. This book of operative gynaecology, published posthumously, was his last work and it bears witness to his courage and determination. Those who knew him well will find in this volume a reminder of his personality and his strongly-held views. Those who never came into contact with him will find evidence of his originality of mind, of his pursuit of knowledge and of his versatility in both the theory and the practice of gynaecology; while his preface will give them more than a hint of his character and of his high standards.

The book is based on a definite plan. It was felt that readers would not require detailed descriptions of instruments, operating theatre techniques or simple surgical methods. The temptation to overload it with references and statistics was to be avoided. References are therefore relatively few, and those older statistics are omitted which modern surgical methods have robbed of their relevance to present-day results. Consequently the book, which includes a chapter on Caesarean section and hysterotomy, is best described as fairly comprehensive rather than as encyclopaedic. Indeed it is a compliment to say that this work might be better entitled "Essays on Operative Gynaecology", especially as the text is not restricted to operative techniques but includes discussion of alternative methods of treatment.

It follows that it is not difficult to pick out those aspects of gynaecology in which Shaw was particularly interested. The author may have recognized this, for in his preface he states frankly that the chapter on "Anatomical Considerations" is deliberately provocative. Some readers will no doubt find other sections equally provocative, whether deliberately or otherwise. For example, Shaw feels that the Spalding-Richardson operation of subtotal vaginal hysterectomy will replace vaginal hysterectomy in the treatment of prolapse, with Fothergill's operation being restricted to cases where the uterus must be conserved. Again, some will not approve his preference for radiotherapeutic castration over radical surgery in extensive or recurrent endometriosis; nor follow his advice that in the repair of a vesico-vaginal fistula a Martius graft should be interposed almost as a routine.

Throughout, the author puts his views clearly and firmly; but he makes no extravagant claims for the particular techniques he has devised or favoured, and alternative measures are described with equal detail. The advantages of modern methods of pre-operative and post-operative treatment are emphasized, but the chapter on post-operative complications might have been enlarged with profit. The reader might also wish for more critical evaluation of tubal patency tests, and for guidance on such points as to how soon after myomectomy pregnancy might be attempted, and whether and when the ovaries should be removed routinely at the time of hysterectomy.

The illustrations, most of which were drawn by Leslie Caswell, are excellently reproduced, and the publishers are to be greatly complimented on producing a book whose beauty makes it a joy to handle. The author could have wished no finer tribute.

"Atlas of Exfoliative Cytology." By GEORGE N. PAPANICOLAOU, M.D., Ph.D. With 36 colour plates and 48 references. The Commonwealth Fund, Harvard University Press, Cambridge, Mass. Geoffrey Cumberlege, London, 1954. Price 144*s*.

ONLY eleven years have passed since Papanicolaou and Traut published their standard book on *The Diagnosis of Uterine Cancer by the Vaginal Smear*, but early cancer diagnosis by means of exfoliative cytology has developed into a science of its own since then. In his new *Atlas of Exfoliative Cytology*, which is conveniently brought out in the style of loose leaf notebooks, Papanicolaou tells this story briefly and gives an excellent illustrated account of the present applications and limitations of cyto-diagnosis. Cytology has travelled a long way from its early confinement to the female genital tract; it now comprises, in addition, the upper respiratory tract, the alimentary and urinary systems, breast secretions, the prostate and the male genital tract, as well as pleural, pericardial and ascitic fluids.

After a short preface and a technical section which deals with apparatus and detailed instructions about collection, preparation and staining of smears, the main section of the atlas is devoted to cytology proper, i.e., the morphology of exfoliated epithelia in health and disease. It is a remarkably complete book. Papanicolaou manages to acquaint the reader with every known type of exfoliated cell and its variations, with the aid of only 36 colour plates. These are indeed exquisite. Twenty-four are drawn by the artist Hashime Murayama and twelve are photomicrographs, each plate comprising a variety of cells and cell groups as found in smear types. Non-malignant and malignant cells are segregated as a rule, but a few exceptions have been made to allow for comparison. Drawings and photomicrographs impress by their clarity and attention to minute detail.

This book, despite its high cost, will prove indispensable in every cytological laboratory as a reference volume as well as an inexhaustible source of information.

E. Wachtel

"Paediatric Gynaecology." By GOODRICH C. SCHAUFFLER. Third edition. Pp. xiv+308. With 76 illustrations. Published by Interscience Publishers Limited, London, 1953. Price 57*s*.

THIS is the third edition of Dr. Schauffler's well-known book of *Paediatric Gynaecology* (first published in 1942). It was written with the object of presenting the accumulated knowledge on the anatomy, physiology and disorders of the female genital tract from birth to puberty. The scope of the book is widened and its value increased by the introduction of chapters on general surgical considerations, urology, proctology, social and medico-legal aspects.

The present edition has been enhanced by the addition of a new chapter on embryology of the genital tract. The chapter on the aetiology and management of vaginitis has been rewritten in the light of further experience and that on menstruation and its disorders has been re-examined and largely rewritten.

The subject matter of the text is in general uniformly good but could be improved by the deletion of methods of treatment which have been proved of doubtful value. This applies particularly to the treatment of delayed menarche, dysmenorrhoea and puberty bleeding. It is surprising that no mention is made of cyclical oestrogen-progestogen therapy, which many clinicians have found to be so useful in puberty bleeding.

These are minor criticisms which do not detract from the value of the book which is easily read and well illustrated. It can be warmly recommended not only to gynaecologists but to all physicians and surgeons who have children under their care.

"The Hypertensive Disorders of Pregnancy." By ERNEST W. PAGE, M.D. Pp. xiv+120. Charles C. Thomas, Springfield, Illinois, U.S.A., and Blackwell, Oxford, 1953. Price 27*s*.

DR. ERNEST PAGE'S book *The Hypertensive Disorders of Pregnancy* is a welcome addition to current medical literature. In a mere 120 pages, he brings order out of chaos and in an engagingly fresh style holds our unflagging interest—even those of us who are wearied by the interminable output of books and papers on the toxaemias of pregnancy.

The book consists of an introduction, three chapters and an excellent critical bibliography. Most of the larger textbooks of obstetrics cannot usually devote sufficient space to this important subject and the aspirant for knowledge has, as a rule, to turn to the specialized textbooks on toxaemia which are commonly so overloaded with alleged facts that he cannot see the wood for the trees. Dr. Page's book is an ideal compromise. In it will be found all that is necessary to bring oneself up to date with current views and researches.

In his introduction he discusses the problem of nomenclature and the one he uses will be found acceptable to most obstetricians. He retains primary renal disease (nephritis) in the classification and with this we are in full support. Two additions are made to the usual classification into the three groups of specific toxaemia, essential hypertension and nephritis and these are—"generalized oedema of pregnancy" and "post-toxaemic recurring hypertension in multiparae". With regard to generalized oedema, it is well known that virtually all pregnant women develop some oedema—occult or overt. Dr. Page believes that, although water and salt retention is common in pregnancy and clinical oedema can be detected in over half of our patients and be regarded as virtually physiological, we should regard more widespread oedema as being likely to predispose to pre-eclampsia. He emphasizes, however, that we only suspect this and cannot be quite certain that prevention or treatment of oedema will prevent the onset of toxaemia, a view with which many of us are in entire agreement. The clinical entity "post-toxaemic recurring hypertension in multiparae" would seem to correspond to our British notion of "recurrent pregnancy toxaemia"—a condition largely determined by a slowly developing essential hypertension.

Chapter I deals with clinical aspects of toxaemias in a fresh and original way. All teachers of obstetrics will be delighted by Table III in which anti-toxaemia insurance premiums payable by certain categories of pregnant women are set forth. The obese, diabetic, hypertensive woman who has twins is shown to be virtually uninsurable! The treatment of eclampsia is very fully dealt with and the rationale of the various methods used fully explained. Dr. Page is rightly cautious in advocating the use of the various hypotensive drugs in the non-convulsive cases for few have yet had sufficient experience to be dogmatic, but there would seem to be a real field for the use of intravenous Apresoline. This chapter will prove of great interest even to the most experienced and blasé obstetrician.

Chapter II gently takes the reader through all the known physiological and biochemical changes in normal and toxaemic pregnancy. The book was in the press before Professor McClure Browne's work on placental circulation was published but the various methods whereby uterine blood flow can be affected are described.

Finally, in his third chapter, Dr. Page attempts the task of discussing the aetiology of toxaemia. Being a wise man he commences by pointing out that in dealing with aetiology we must separate certain factors. *Predisposing factors* such as diabetes and heredity hypertension are only important in that they tend to predispose the patient to toxaemia. The diabetic woman does not by any means always develop toxaemia. The *precipitating factor* is clearly the uterus and its contents for, although every pregnant woman does not develop toxaemia, she cannot develop toxaemia without a pregnancy. The *proximal cause* is likely to be a chemical mediator circulating in the blood which exerts major effects on the kidney, heart, liver and placental site and gives rise to the *secondary manifestations*. He then discusses these various factors and sums up by assembling the many arguments which tend to favour the hypothesis associated with his own name—that of uterine ischaemia.

Dr. Page has made many important contributions to clinical and academic obstetrics and not the least of these will be this short book. It makes good reading for all interested in obstetrics be he an undergraduate or a

senior consultant. We should certainly ensure that our medical colleagues read it and all men working in laboratories on the problem of toxaemia. Readers in this country will be impressed by the handsome references he makes to the British literature on this subject.

R. J. Kellar

"Toxaemias of Pregnancy." By JOHN SOPHIAN, M.D., F.R.C.S. Pp. xiii+231. With 37 figures. Butterworth and Co., London, 1953. Price 25*s*.

IT is many years since a British obstetrician has been brave enough to write a book on the toxaemias of pregnancy. There are indeed few who have the necessary erudition and experience to do so. Dr. John Sophian, whose enthusiasm, profound knowledge of the literature and record of sound research, has long been admired by serious students of this difficult subject, has essayed this difficult task and has succeeded in giving us a very useful and readable account of the whole problem.

It is difficult to select any particular portion of the book for detailed discussion as Dr. Sophian gradually builds up his thesis of the vital importance of renal dysfunction in the genesis of the main features of the disease. A discussion of the embryology of the kidneys and uterus is followed by a detailed and lucid account of the Trueta shunt mechanism and of Dr. Sophian's and his collaborators' experimental work on the utero-renal reflex. The various mechanisms, whereby increased uterine tension may cause renal cortical shut-down, are fully discussed. Having shown that abnormal renal circulation can and does occur, he then proceeds to analyze normal renal function and disorders of that function in toxaemia. Those who find their knowledge of sodium metabolism in pregnancy woefully inadequate, will find much profit in reading this section of the book. In the chapter devoted to hypertension the author describes various known pressor substances such as angiotonin and vaso-excitor motor substance (V.E.M.) and comes to the conclusion that these are probably responsible for the hypertension of toxaemia and are liberated in excess during renal cortical ischaemia. The role of cerebral dysrhythmia in the genesis of eclampsia and the factors affecting this phenomenon are clearly described. The clinician will be particularly interested in Dr. Sophian's remarks on the treatment of pregnancy toxaemia. Here the importance of getting rid of excess body sodium is stressed and the use of exchange resins critically analyzed. He takes his colleagues in this country gently to task for being reluctant to employ conduction anaesthesia in the eclamptic patient. It is pointed out that when the effect of the anaesthetic reaches D.10 and D.11 there is usually a dramatic improvement in the patient's condition for at this level there is an "anaesthetic denervation" of the kidney, a fall in blood pressure and diuresis occurs. The last two chapters of the book deal with the conditions of concealed accidental haemorrhage and anuria and modern methods of handling the latter complication are fully treated.

Dr. Sophian deals fairly and critically with the older concepts of the disease but throughout the book he develops an extremely strong case for the thesis which he presents, namely, that increased uterine tension leads to renal dysfunction and ultimately to the well-known clinical features of the disease. This book must certainly be read by all those who wish to obtain a real insight into our present-day knowledge of the toxaemias of pregnancy.

R. J. Kellar

"Historical Review of British Obstetrics and Gynaecology 1800–1950." Edited by J. M. MUNRO KERR, R. W. JOHNSTONE and MILES H. PHILLIPS. Pp. viii+420. E. & S. Livingstone, Ltd., Edinburgh and London. Price 30*s*.

THIS book, which is a gift to the College on its Silver Jubilee, has been written by senior fellows under the general guidance of J. M. Munro Kerr, R. W. Johnstone, and Miles H. Phillips. It is a sequel to H. R. Spencer's *History of British Midwifery, 1650–1800* and covers the years 1800 to 1950.

It starts with a general Obstetrical Review by the Editors, covering the three fifty-year periods under the main headings: "Anatomy and Physiology", "Pregnancy", "Labour", "The Haemorrhages", "Injuries of the Birth Canal", "Pelvic Malformations—Pelvimetry", and "Obstetric Operations". Then there are twelve chapters dealing with special subjects in Obstetrics: "The Initiation and Development of Antenatal Care", "Toxaemias of Pregnancy", "Pregnancy and Associated Disease", "Complications Associated with the Utero-Vaginal Canal", "Puerperal Infection", "Obstetric Anaesthesia and Analgesia", "Radiography in Obstetrics and Gynaecology", "Maternal Mortality—Stillbirth and Neonatal Mortality", "The Medical Schools and the Teaching of Midwifery", "Obstetrical Societies and Clubs", "Journals 1800–1950", and "Midwife Services". Finally, there are four chapters on Gynaecology: "The Rise of Surgical Gynaecology", "Plastic Vaginal Surgery", "The Progress of Radio-therapy in Gynaecology", and "The Sex Hormones in Gynaecology".

In reading this timely history of our specialty, one is naturally and easily carried back to student and resident days when one was introduced to the subject; early impressions are re-awakened and there are many reminders of our early teachers, to whom we owe so much. The names of the contributors are household words to those of us in practice, and it is most stimulating to read their contributions. If any criticism is to be made it might be that in one or two chapters the names of British obstetricians and gynaecologists are difficult to find among the multitude of foreign names; certainly credit must be given where it is due, but surely in a History of British Obstetrics and Gynaecology the emphasis should be on the efforts, however modest, of our own countrymen. Once or twice an important contribution by a British worker has been overlooked.

This is a treasure house of a book with many valuable pieces: there are the welcome pages in which we are kindly but firmly shown how to practise our specialty; there are the sections which remind us of our heritage and give us a proper pride in our own folk; there are large sections packed with information giving a very complete picture of particular scenes; and there is the

high quality of arrangement and reproduction. These are worthwhile matters, but they may be thought only temporary. This book has a permanence about it which arises from the fact that it is a considered and personal expression by men of wide understanding and experience and of high renown. To British obstetricians and gynaecologists it will mean even more: it is a token from senior colleagues of their faith in British Obstetrics and Gynaecology, and is an encouragement to those who follow. If we learn from the mistakes and triumphs of the past we may play our part with distinction.

In great part the gift-book has been rendered possible through the generosity of the publishers, Messrs. E. & S. Livingstone, who have generously offered to present all profits on the sale to the Royal College of Obstetricians and Gynaecologists.

C. Scott Russell

"Annual Report on the Results of Treatment in Carcinoma of the Uterus." Ninth Volume. Pp. 256. Statements of Results obtained in 1947 and Previous Years. (Collated in 1953.) Editorial Office: Radiumhemmet, Stockholm 60.

THE 9th Report in this series contains statements on cervical carcinoma from 72 institutions, 67 of which were collaborating also in the previous Report, covering 87,424 patients from 17 different countries, of whom 81,576 (93 per cent) were treated. These form Part I of the Report. Statements on carcinoma of the uterine body were submitted by 19 collaborators in 10 different countries, comprising 5,480 patients. These form Part II of the Report. Part III deals with 637 cases of carcinoma corporis and endocervicis, carcinoma uteri et ovarii and carcinoma pelvis, submitted by 12 contributors. In contrast to the 6th and 7th volumes in this series, the scope of these Reports has not been increased further and only 2 new chapters concerning terminology have been added. One deals with suggestions concerning alterations of the definitions of the four stages in cervical carcinoma and one is an entirely new idea, presented under the heading "Collaborators' Corner"; it contains extracts of discussions relating to adequacy and comparability of therapeutic statistics on uterine carcinoma.

Part I, dealing with carcinoma of the cervix, is subdivided into 5 parts according to stage grouping. Unfortunately, the section on stage O carcinoma is very short as only 3 out of 22 contributors report on a number of cases sufficiently large to be of statistical value and evaluation of results is, therefore, postponed until more material can be analyzed.

As in previous years, the relative apparent recovery rate of stage I–IV carcinoma of the cervix at the end of 5, 7, and 10 years is worked out in admirably compiled tables, detailing the results of the 72 individual contributors. There is a very striking variation in recovery rate, e.g., the highest 5-year apparent recovery rate of stage I carcinoma of the cervix is reported from the Radium Institute, Montreal (86·4 per cent) and the lowest from Glasgow (38·5 per cent). The discrepancy in 10-year results is equally remarkable, varying from 76·5 per cent (Lund, Sweden) and 6·9 per cent (Montpellier). It would be of paramount importance to find an explanation for these extreme differences in therapeutic results.

The overall relative apparent recovery rate in this Report (34·7 per cent) is the highest yet presented in this series, showing a steady rise from 26·3 per cent in volume 2. This is due chiefly to an increase in apparent recovery rate in all stages and also to a slightly reduced proportion of advanced cases.

Comparisons between results obtained by primary surgical treatment and by sole employment of radiotherapy show no significant differences. Institutions in favour of primary hysterectomy in selected cases obtained an apparent recovery rate of 62·5 per cent in stage I, 42·7 per cent in stage II and 49·8 per cent in stage I and II. The corresponding figures at institutions favouring primary radiotherapy are 65·3 per cent, 45·9 per cent and 51·8 per cent respectively.

The second part of the Report deals with carcinoma of the corpus uteri. The submitted material is presented in the same way as the cervical cancer cases, i.e., in a combined table as figures supplied by all collaborators and separate statements furnished by the individual collaborators. The material comprises 58 cases of stage O carcinoma, all of which received treatment, 48 having been given radiotherapy and 10 surgical treatment. Five patients developed invasive carcinoma within a 5-year observation period. Four of these after radiotherapy and 1 following hysterectomy. Three died of intercurrent disease and the remaining 50 patients are alive and symptom-free.

Analyses of stage I (group 1 and 2) and stage II carcinoma of the body are made in detail, although the submitted material is still small. Comparing the results of primary hysterectomy and radiotherapy no significant differences are found, the figures being 54·5 per cent and 53·5 per cent apparent recovery rate. No definite conclusions can, however, be drawn from these figures as the total number of cases is small, as the probability of a certain degree of selection is high and as the various statements are not related to the same period of time.

Part III deals with carcinoma corporis et endocervicis, carcinoma uteri et ovarii and carcinoma pelvis. The material, submitted by 12 collaborators, is still too small to be of statistical significance. The proportion of cases referred to each of the 3 groups varies only slightly from the tables in the 8th Report.

The present Report will be of great interest to all those engaged in the treatment of cancer of the female genital tract and, as in previous years, a wealth of information is compiled in this small book of 256 pages. The material is admirably presented in tables easily understood by people without special training in statistical methods. Detailed summaries of overall results in the final chapter of the book will prove useful for rapid information on the present day position in cancer therapy of the uterus.

E. Wachtel

REVIEW OF CURRENT LITERATURE

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ANATOMY AND PHYSIOLOGY

216. The Contracted Midpelvis.

By S. HANSON. *West. J. Surg. Obstet. Gynec.*, **61**, 628–632. Nov. 1953. 20 refs.

The author reviews his contributions to the literature in this subject over the past 23 years. The study of the mid-pelvis is made easier by dividing it into two parts, the "lower mid-pelvis" at the ischial spines, and the "upper mid-pelvis" above this level. The narrow inter-spinous diameter is important in the aetiology of occipito-posterior positions and is a cause of low cavity arrest in primiparae. The width of the upper mid-pelvis can be estimated from the transverse diameter of the brain and the diameter between the bases of the lochial spines; this width should be about 11·6 cm. Contraction of the upper mid-pelvis is an important factor in the production of high occipito-posterior arrest and a serious obstruction to high mid-forceps delivery.

[This paper is difficult to abstract; the original should be consulted for further details.]

D. C. A. Bevis

217. The Vascular Bed of the Bulbar Conjunctiva in the Normal Menstrual Cycle.

By R. LANDESMAN, R. G. DOUGLAS, G. DREISHPOON and E. HOLZE. *Amer. J. Obstet. Gynec.*, **66**, 988–998. Nov. 1953. 7 figs. 17 refs.

The bulbar conjunctivae of 15 normal women between the ages of 18 and 26 years were viewed daily through the menstrual cycle with a slit lamp and binocular microscope. From ovulation to menstruation the vessels become engorged and dilated; immediately before the onset of the menstrual flow vasoconstriction of the arterioles occurs and usually continues for about 3 days after which vascularity increases. Six photographs are included illustrating the vascular changes during the cycle.

F. J. Browne

PREGNANCY

218. Nutrition in Prenatal Care.

By F. E. WHITACRE. *J. Amer. med. Ass.*, **155**, 112–114. May 8, 1954.

As a result of clinical impressions from many parts of the world the author discusses the nutritional factor in pregnancy from a practical standpoint. Toxaemia of pregnancy is one of the most vital problems and most often seen in patients with nutritional deficiencies. Excessive weight gain is to be avoided, and it is seldom that the patient who has been carefully controlled as to weight gain will have severe complications. A maximum of 20 pounds gain for the 40 weeks of pregnancy is recommended. The average patient should have from 2,500 to 3,000 calories per day, with about 90 g. of protein, 250 g. of carbohydrate, and 130 g. of fat. This, however, is not understood by most patients nor by a large number of physicians, and it is better to make simple suggestions such as those found in Canada's food

rules for normal pregnancy. This diet, which is described briefly, contains all the essential minerals and it is unnecessary to supplement it except that in the winter months vitamin D may be added. The author believes that proper weight control and a balanced natural diet in pregnancy will reduce the incidence of hypochromic anaemia and toxaemia.

D. W. James

219. **Frequency and Significance of Bleeding in Early Pregnancy.**

By H. SPEERT and A. F. GUTTMACHER. *J. Amer. med. Ass.*, **155**, 712–715. June 19, 1954. 16 refs.

Comparative embryological studies have shown that bleeding from the genital tract often accompanies the early stages of placentation and embryonic development in many species of vertebrates. After summarizing the evidence for this phenomenon in the lower vertebrates and placental mammals the authors present evidence for its occurrence in human pregnancy.

Single vaginal smears were taken at random from 68 women between the 33rd and the 60th days of pregnancy. After excluding lesions of the cervix and vagina 12 of the 68 smears showed the presence of red blood cells. Only 1 of the 12 patients with a positive smear aborted. The occurrence of macroscopic vaginal bleeding between conception and the 196th day of pregnancy was investigated in another series of 225 patients. Bleeding was reported in 49 patients and in 42 of these it was considered to have been of physiological origin. In 18 cases bleeding was limited to a single episode on or before the 40th day of pregnancy and this may have represented a physiological response to implantation. The differentiation of physiological and pathological bleeding is made by clinical considerations. The physiological bleeding of early pregnancy is distinguished from the bleeding of abortion by the usual association of abortion with a greater flow of blood, the brown-black colour of the initial vaginal discharge, uterine cramps, and the absence of nausea.

Although the series of cases is small, the fact that single smears taken at random in the first series showed 18 per cent with red blood cells suggests that this would be a minimum figure. The authors conclude that physiological microscopic bleeding from the uterus actually occurs with greater frequency, and that it occasionally assumes macroscopic proportions which may even simulate the menstrual flow. Although no treatment is required it may cause difficulty in calculating the duration of pregnancy.

D. W. James

220. **Pelvic Insufficiency During Pregnancy and After Parturition.**

By D. BEREZIN. *Acta obstet. gynec. scand.*, **33**, Suppl. 3. 1954. 156 refs.

The term "pelvic insufficiency" (p.i.) is applied in this monograph of 119 pages which comes from Malmö and Norköpping (Sweden) to a condition appearing during pregnancy or in connexion with parturition, and characterized by pain and tenderness of the pelvic joints and by impairment of locomotor function. The symptoms of p.i. initially appearing during pregnancy are ascribed to the hormonally induced relaxation of the pelvic joints ("relâchement douloureux"). P.i. first appearing in association with a delivery is conceived as an injury sustained during parturition. Although the two conditions are regarded as separate clinical entities, clinical observations suggest that a certain predisposition is usually necessary for such an injury to occur, and that this predisposition might be identical with pelvic relaxation. Both conditions showed a certain seasonal variation, both appearing more frequently during the winter months.

The purpose of this paper is firstly to direct attention to the local pelvic manifestations and associated static trouble of p.i., and secondly to study symptoms which, though not specific of p.i., were found to be common in this condition, namely tetany, acroparaesthesia, cramps, meralgia paraesthetica, and osteitis condensans ilii.

The author's material consisted of 142 cases, 66 of which were of the type p.i. during pregnancy, and 76 of the type p.i. after parturition.

[The wealth of clinical and statistical data presented in this monograph does not lend itself to abstracting, but this thoughtful paper deserves to be read in its entirety.]

N. Alders

221. **The Hypertensions of Pregnancy.** (Considerazioni sulle sindromi ipertensive in gravidanza con particolare riferimento alla ipertensione essentiale.)

By M. BOSCARO. *Minerva Ginec.*, 187–198. March 31, 1954. 66 refs.

Hypertension can be casually associated with pregnancy or can be directly related to it, and the pathology, prognosis maternal and foetal, progress and treatment differ depending on the group to which the hypertension belongs.

Hypertensions of Pregnancy. (1) Hypertensive nephropathy of pregnancy: systolic blood pressure above 140 with an equivalent rise in the diastolic blood pressure, appearing about the eighth month and shortly preceding albuminuria with casts, oedema and ocular disturbances. These cases often lead to premature delivery and birth of a stillborn foetus. (2) Pre-eclampsia and eclampsia: the pressure rises continuously to 150–200 systolic and 90–140 diastolic, associated with oliguria, albuminuria, headache, with visual and psychic disturbances often proceeding to eclamptic convulsions. (3) Post-toxaemic hypertension: a continuance often progressive and very severe of a hypertension initiated in pregnancy. Any subsequent pregnancy may lead to fatal aggravation and acute uraemia. It is distinguished from chronic glomerulonephritis complicated by pregnancy by arising in young women who are known to have been quite healthy prior to a pregnancy in which hypertension and albuminuria developed and who have been affected since the pregnancy in question by no other illness which could have led to the syndrome. Using as a type a woman aged less than 40 with a blood pressure of 150/100 over a period

of 2 to 4 years, the author quotes a view that toxaemia of pregnancy is followed by this condition in 31·4 per cent of cases. (4) Renal cortical necrosis: acute lumbar pain, anuria, uraemia and death. It supervenes occasionally on pregnancy toxaemia. (5) Essential hypertension of pregnancy—(to be contrasted with essential hypertension in pregnancy dealt with under (9) below). It was found in 3 per cent of all pregnancies. Its subjects are usually young women up to 30 years of age, giving no previous history of hypertension or other relevant disease but often with such predisposing factors as overweight or a family history of "blood pressure". The condition manifests itself about the middle of pregnancy, usually in primiparae. Other signs of toxaemia are absent or slight and non-progressive. The pressure rarely rises above 160 to 170, and returns as a rule to normal after delivery. Subsequent pregnancies are usually but not always accompanied by a recurrence of the hypertension at the same or a slightly higher level. In mild and uncomplicated cases pregnancy can proceed to term without detriment to mother or child. The condition appears to be due to a temporary upset of hormonal balance (hyper-postpituitarism) or to overaction of the sympathetic, but the cause cannot be considered as settled.

Hypertensions in Pregnancy. (1) Acute glomerular nephritis characterized by haematuria with coffee-coloured urine, oedema and hypertension. (2) Toxic nephrosis: anuria often preceded by a transient polyuria of a urine heavily loaded with albumen. Oedema is infrequent. In pregnancy early abortion occurs. (3) Chronic glomerulo-nephritis. In the absence of a reliable history this is difficult to diagnose from the hypertension of mild pre-eclamptic toxaemia. (4) Chronic pyelonephritis: often liable to relapses and exacerbations in pregnancy. (5) Vascular nephrosclerosis: rare in pregnancy, being a disease of the later years. (6) Polycystic disease: rarely associated with pregnancy. (7) Hyperadrenal hypertension: can be distinguished by pharmacological tests. (8) Hypertension associated with aortic coarctation. (9) Essential hypertension in pregnancy. This accounts for 12 per cent of all the hypertensions found in pregnant women. The blood pressure is raised before pregnancy starts, is unaccompanied by any renal disorder but with some cardiac hypertrophy and left deviation in the ECG. It occurs usually in women in the thirties and forties. In nearly half the cases the pressure remains constant throughout the pregnancy. In at least a third it tends to fall about the fifth month, but to rise again at the end. In the remainder a pre-eclamptic state develops after the sixth month. In the first group a definite oedema is usual. In the second, it is suggested that the fall is due to the easy arterio-venous flow at the placental site, its rise at the end coinciding with the increasing sclerosis and muscular tension at the same site. In the third group, a developing pre-eclamptic syndrome brings much increased risk to the life of both mother and baby, but in general the termination of the pregnancy in all three groups, whether spontaneous or induced, premature or at term, is followed by a return of blood pressure to a level little or no higher than that which existed before the patient became pregnant.

In the article here reviewed, full clinical histories are given of 5 cases illustrating some of the above types, and the appropriate treatment whether by diet, rest, drugs, induction or Caesarean section is discussed.

W. C. Spackman

222. Does the Administration of Diethylstilbestrol during Pregnancy have Therapeutic Value?

By W. J. DIECKMANN, M. E. DAVIS, L. M. RYNKIEWICZ and R. E. POTTINGER. *Amer. J. Obstet. Gynec.*, **66**, 1062–1081. Nov. 1953. 9 tables. 5 figs. 11 refs.

In 1946 Smith and Smith of Boston (*Amer. J. Obstet. Gynec.*, **51**, 411) suggested, as a result of observations on a series of primigravidae, that increasing amounts of diethylstilboestrol administered in pregnancy diminished the incidence of toxaemias, of postmaturity, prematurity, and unexplained stillbirths and neonatal deaths, but the present authors from Chicago criticize the experiment because of alleged lack of adequate controls. They carried out an experiment of their own in which 840 women took graduated amounts of diethylstilboestrol according to the schedule devised by Smith and Smith, beginning before the 20th week and continuing for at least 5 weeks, the average duration of the treatment being 15 weeks, and the average time of entry into the study being 11·5 weeks for the primiparae and 12·5 weeks for the multiparae. The controls were 806 women who took similar tablets but containing only a placebo. As a result it was considered that the stilboestrol did not reduce the incidence of any of the above mentioned conditions.

In the discussion that followed this communication the Smiths vigorously maintained their original claim for stilboestrol, and in turn criticized the Chicago experiment, especially in regard to selection of the participating women. The other speakers seem to have supported the Smiths or the reverse according to whether they came from Boston or not.

F. J. Browne

223. Cerebral Circulation and Metabolism in Toxemia of Pregnancy. Observations on the Effects of Veratrum Viride and Apresoline (l-Hydrazinophthalazine).

By M. L. MCCALL. *Amer. J. Obstet. Gynec.*, **66**, 1015–1030. Nov. 1953. 6 tables. 88 refs.

The author studied cerebral blood flow by the nitrous oxide method in 325 pregnant women, normal and toxaemic. In normal pregnancy cerebral blood flow, cerebral oxygen metabolism, cerebral vascular resistance and respiratory quotient are almost the same as in non-pregnant persons, but arterial and venous concentrations of oxygen are much lower, apparently owing to pregnancy hydraemia. In toxaemia cerebral blood flow is not affected, though the method used measures only the overall cerebral blood flow, and gives no information regarding isolated areas of the brain. Cerebral oxygen metabolism is normal in non-convulsive toxaemia but is depressed during the coma of eclampsia. This lowered oxygen consumption is present even though the arterial oxygen supply to the brain is normal, suggesting a histotoxic anoxia. Cerebral vascular resistance is increased in both convulsive and non-convulsive toxaemia,

thus supporting the view that in toxaemia there is generalized vascular spasm. Veratrone lowered both the arterial blood pressure and cerebral vascular resistance, while cerebral blood flow, cerebral oxygen metabolism, respiratory quotient of the brain and the blood gases remained normal. Apresoline decreased mean arterial blood pressure and cerebral vascular resistance and increased cerebral blood flow and oxygen utilization by the brain. The respiratory quotient of the brain and the blood gases remained normal.

F. J. Browne

224. **Hydatidiform Mole.** (Mola hidatiforme.)

By A. J. Guiroy and E. Koremblit. *Obstet. Ginec. Lat-amer.*, **11**, 485–493. Nov.–Dec. 1953. 87 refs., no figs.

The authors report on their survey of all the case records of hydatidiform mole which have occurred in their hospital between the years 1928 and 1952: these amount to 68 cases in 145,889 pregnancies.

After a detailed historical survey, the authors discuss the statistics of their own survey. They found that 66 per cent (45 cases) of their series were in multiparae, and that 72 per cent (52 cases) occurred between the ages of 20 and 40: only 2 hydatidiform moles were found before the age of 20, and 14 after the age of 40.

In a brief reference to the aetiology of this condition, the authors quote the work of De Ruyk, who believed from his own experiments that a hydatidiform mole was due to a filterable virus.

Vaginal bleeding was the main symptom in 62 cases. Ovarian cysts, presumably theca-lutein, were only palpated in a third of the patients, and these cysts were mainly small. Considerable confidence is expressed in the work of Pigeaud and Burthiault, who claim that pregnanediol is found for several days after the removal of a hydatidiform mole, and that, if pregnanediol is found as long as 15 days afterwards, malignant changes should be suspected. The same workers are also quoted as stating that, if pregnanediol is found after an apparently straightforward spontaneous abortion, examination of the conceptive products may reveal microscopical evidence of hydatidiform mole.

Only 6 cases in the series under review became malignant, and 4 others died of sepsis in the early years of the survey period before the discovery of antibiotics. Forty-two patients expelled the mole spontaneously.

The authors draw no conclusions after presenting their findings; they state however that from their observations of these 68 cases, delivery of a hydatidiform mole by the vaginal route gives satisfactory results.

John F. Foulkes

225. **Placenta Previa and Previous Lower Segment Caesarean Section.**

By S. Bender. *Surg. Gynec. Obstet.*, **98**, 625–628. May, 1954. 10 refs.

During the course of an enquiry into the causes of bleeding in placenta praevia it was noted that several of the multiparas with placenta praevia had had a previous lower segment Caesarean section. In order to ascertain whether this was a chance finding or one of possible aetiological significance, the author has reviewed all cases of placenta praevia seen in the hospitals in Liverpool during approximately 6 years, together with those admitted to the Royal Maternity Hospitals, Belfast, during a similar period.

There were 444 multiparous patients with placenta praevia and of these 45 (10 per cent) had had previous Caesarean section of the lower segment type. This proportion showed very little variation from hospital to hospital and compared with an incidence of previous section of 3·8 per cent in all multigravidae delivered in hospital during the same period.

In 67 per cent of the 45 cases of placenta praevia following section the placenta involved the anterior surface of the lower segment, whereas in other cases of placenta praevia the anterior wall was involved in only 30 per cent.

It is suggested that a lower segment section scar may predispose to placenta praevia occurring in a subsequent pregnancy, especially the one immediately following the section, and perhaps particularly if the time interval from delivery to delivery is 2 years or less.

The author thinks that it may be possible that the vascularity of the region of the scar is so altered that, if the site of a subsequent implantation is relatively low, the persistence of villi of the chorion laeve in contact with the scar is encouraged, perhaps because of better penetration.

If these figures are confirmed by others, several points of interest arise. Firstly, as the lower segment is increasingly the route of choice for section, the incidence of placenta praevia may rise. Secondly, with an increasing proportion of cases of placenta praevia being treated by lower segment section, the incidence of recurrent placenta praevia may rise. Thirdly, a further reason becomes apparent why there should be no relaxation of the indications for Caesarean section, an operation which always prejudices the woman's obstetric future. And, fourthly, not only should every woman with a section scar always be delivered in hospital, but placentography is indicated in each pregnancy, especially in those instances in which vaginal delivery is contemplated.

John P. Erskine.

226. **Unusual Result of a Procured Abortion.** (In tema di aborto procurato, rarissima esito di manovre abortive.)

By Ugo Lo Conte, *Minerva Ginec.*, 42–43. April 15, 1954.

A case is detailed of a woman who secretly attempted to introduce a gum-elastic catheter into her uterus to procure abortion. She was admitted (on 13th March) for pain in the left iliac fossa and a purulent discharge from the vagina for the past 3 days. She was about 3½ months pregnant and the pain and discharge were increasing; she gave an obviously fallacious and misleading history.

A doughy lump the size of a fist was felt in the left parametrium and a small hole was seen in the posterior fornix discharging a little saneous pus. There was a slight degree of fever. The patient was treated with penicillin which diminished the symptoms and the size

of the lump, and the patient insisted on leaving the hospital on the eighth day of treatment. The patient aborted at home 3 days later (26th March). On 10th April the uterus was normal, the vaginal sinus closed, but the infiltration in the left iliac fossa was still present; the patient had a normal menstruation on the 30th April.

On 13th May in her own home she noticed a small blister near the left anterior superior iliac spine which she swabbed with alcohol, pricked with a needle and withdrew a gum-elastic catheter which she later triumphantly produced before her solicitous gynaecologist. On clinical examination, apart from a tiny scar marking the exit of the catheter, no trace of her adventure could be found.

W. C. Spackman

227. **Cardiovascular Problems in Pregnancy.**

By B. E. HAMILTON. *Circulation*, **9**, 922–933. June 1954. 34 refs.

Dr. Hamilton states that those who give advice to pregnant cardiac patients must be prepared to discuss (1) maternal and infant death rate; (2) the risk of immediate invalidism; (3) whether maternal heart disease injures the infant; and some lesser specific questions.

Rheumatic heart disease has a maternal mortality, as reported from various clinics, of less than 1 per cent to more than 3 per cent. In the severely handicapped (Classes III and IV of the New York Heart Association classification), those with complications such as auricular fibrillation and beyond 35 years of age, the load of pregnancy leads to a higher maternal death rate, even with the best care. There is a smaller proportion of patients in the unfavourable Classes III and IV and the author asks if this is due to better care of cardiacs, to fewer unfavourable cardiacs undertaking pregnancy, or to a "milder form of, or better controlled, rheumatic fever". He emphasizes the effect of proper prenatal care on the immediate maternal and infant mortality rates in pregnancy of women with rheumatic heart disease.

The author states that during the years when the majority of marriages occur the mortality rate for rheumatic fever in women is much higher among the unmarried.

The author considers that surgery for rheumatic valvulitis during pregnancy is rarely called for if cardiacs receive timely education. For acute pulmonary oedema, severe dyspnoea, chest pain and haemoptysis which recur in spite of medical treatment it is considered hard to justify withholding both termination of the pregnancy and immediate surgical treatment. The author thinks that we need to know much more about the course during the months immediately following cardiac surgery of young women operated upon apart from pregnancy.

The author states that the extent to which pregnancy affects the life course of women with congenital cardiovascular defects is less clearly known than its effect on acquired heart disease.

Bacterial endocarditis responds to modern chemotherapy, but treatment during pregnancy appears somewhat less successful and 2 patients died with multiple haemorrhages: and both foetuses died *in utero* from intracranial haemorrhage. If it is clear that pregnancy is interfering with treatment prompt therapeutic abortion should improve the chance of survival.

D. J. MacRae

228. **Pregnancy Associated with Diseases of the Adrenal Glands.**

By A. B. HUNT and W. M. MCCONAHEY. *Amer. J. Obstet. Gynec.*, **66**, 970–987. Nov. 1953. 3 tables. 20 refs.

This paper from the Mayo Clinic draws attention to the association of various dysfunctions of the adrenal glands with pregnancy. They include 7 cases of Cushing's syndrome, 1 of phaeochromocytoma and 3 of Addison's disease.

In Cushing's syndrome the pregnancy is endangered by chronic hypertension, and foetal death is common, but after treatment of the disease, usually by subtotal adrenalectomy, of the 5 pregnancies in 5 patients all but 1 who had post-operative adrenal insufficiency and aborted at the second month went through pregnancy satisfactorily. The patient with phaeochromocytoma had 2 pregnancies while the disease was active; one pregnancy produced a living normal child, the other foetal death at 6 months. After cure by bilateral adrenalectomy she became pregnant, was treated by cortisone, DOCA, and extra salt, and had a normal pregnancy and delivery. Two of the cases of Addison's disease became evident for the first time in the puerperium, in 1 of them through the development of adrenal crisis with shock and collapse on the 8th day. She responded to intravenous aqueous adrenal cortical extract and a solution of saline and glucose. This case illustrates that in rare instances postpartum collapse may be the first evidence of Addison's disease. Another case did well during pregnancy with maintenance therapy and was delivered of a normal child by Caesarean section on account of abruptio placentae. During pregnancy the 17-ketosteroids increase in patients with Addison's disease as compared with pre-pregnancy tests and this is not due to the foetal adrenals. Patients with adrenal cortical insufficiency therefore usually do well without treatment, but supportive therapy should be available for them during delivery and the puerperium.

Three adrenal states may cause obstetric shock with serious post-partum collapse and death: (1) post-partum crisis in women with adrenal insufficiency; (2) postpartum collapse due to a phaeochromocytoma; (3) acute adrenal cortical insufficiency due to previous cortisone therapy. This last possibility should be borne in mind for every pregnant woman who has had cortisone therapy.

F. J. Browne

229. **Non-Toxaemic Subarachnoid Haemorrhage during Pregnancy, Delivery or Puerperium.**

By P. A. JARVINEN and E. HUHMAR. *Ann. chir. gynaec. fenn.*, **43**, 85–94. 1954. 1 fig. 24 refs.

The author reviews the literature on subarachnoid haemorrhage due to rupture of aneurysm of the circle of Willis. He describes 4 such cases associated with pregnancy, delivery or puerperium and unassociated with toxaemia of pregnancy. In 1 case an unruptured

aneurysm of the middle cerebral artery was demonstrated by angiography. In the other 3, diagnosis was made by the demonstration of blood in the cerebrospinal fluid. Two of the latter were fatal and no autopsy was done and 1 had a blood pressure of 240/190 in spite of the statement that no toxaemia was present.

D. M. Sheppard

230. **Acute Appendicitis in late Pregnancy.**

By R. B. PARKER, *Lancet*, **1**, 1252–1257. June 19, 1954. 4 tables. 20 refs.

The author describes 6 cases of acute appendicitis complicating late pregnancy which occurred between 1950–53. The difficulty of diagnosing this complication of pregnancy is rightly stressed and various aspects of diagnosis are discussed. Only twice was guarding or rigidity noted and release tenderness was not certainly defined in any of the 6 patients. The temperature range was 96·8° to 100° F. and the pulse rate less than 100 only in patients with less than 24-hours symptoms. Only two conditions were considered as alternative diagnoses in the cases. One was concealed accidental haemorrhage and the other was pyelitis. The danger of delaying operation by observing the patient is pointed out. Appendicectomy without interference of the pregnancy is advocated through a high McBurney incision and extending it upwards in the direction of the right loin. The onset of labour may be expected within 48 hours of operation in a good number of patients near term. From a review of published series it would appear that the maternal mortality is 10 times higher in the last 3 months of pregnancy than before that time. The author states that a reasonable suspicion of acute appendicitis at any stage of pregnancy should lead to laparotomy without delay.

H. H. Fouracre Barns

231. **Ectopic Pregnancy—Pregnancy Reaction and Uterine Mucosa.** (Extrauteringravidität, Schwangerschaftsreaktion und Mucosa Uteri.)

By C. VON NUMERS and O. KINNUNEN. *Ann. chir. gynaec. fenn.*, **43**, 95–101. 1954. 23 refs.

An investigation of 145 cases of ectopic pregnancy with regard to duration of haemorrhage and positivity of the Galli-Mainini pregnancy test. Of these cases 80 gave a positive pregnancy test and of 48 cases where curettage had also been performed 20 showed a decidual reaction. It was found that when the patient had been bleeding for less than a week 85 per cent of such cases gave a positive pregnancy test. Of cases that had been bleeding for 3–4 weeks only 50 per cent gave a positive pregnancy test. The authors consider that a diagnosis of ectopic pregnancy cannot be excluded by a negative pregnancy test or absence of decidua on curettage.

D. M. Sheppard

LABOUR

232. **Rhesus Incompatibility: Are There Indications for Premature Induction?** (Sur le traitement de l'incompatibilité sanguine Rh.)

By M. LACOMME. *Minerva Ginec.*, 300–303. May 15, 1954. 1 table.

Current opinion holds that premature delivery increases neonatal mortality and that prematurity favours the development of the complications of kernicterus, but in spite of these arguments the author considers that the procedure is of value in certain cases. He gives the statistics of 140 cases he has collected between 1950 and 1953. Of these cases, in 109 the incompatibility was discovered before or during the pregnancy, and in 39 the diagnosis was only made after delivery.

Taking the 109 women, 44 of these produced in preceding pregnancies 87 dead children of whom 27 died in the 8th month and 55 in the 9th. It appears therefore that 65 per cent of these infants died intra-uterine during the last month before term. Where the Rh negative woman had had a dead child in a previous pregnancy she lost the next in 37·9 per cent of cases if left to term but in only 11·4 per cent where labour was induced at the beginning of the ninth month. Of 31 babies thus induced and submitted to exsanguino-transfusion 27 survived.

Against the argument that the prematurity acts adversely after birth, it can be said that the longer the pregnancy is allowed to go on the worse are the effects of the blood incompatibility on the infant, and the author maintains that the remarkable advance in recent times in the care of prematures justifies us in discounting prematurity alone as a preponderant factor in deciding our attitude to the problem discussed.

It is true that, if the babies born spontaneously before term are considered, the statistics are much less favourable because such babies are probably expelled because they are moribund in any case. The author therefore considers that there is still a good case for inducing labour a month before term at least in those cases where a mother with Rhesus incompatibility has previously had a stillborn child.

W. C. Spackman

233. **Intravenous Ergometrine and the Undiagnosed Second Twin.**

By J. K. RUSSELL, D. TACCHI and A. L. M. GRAHAM. *Brit. med. J.*, **1**, 1129–1130. May 15, 1954. 3 refs.

During the past two years, on 4 occasions an undiagnosed second twin was discovered after the administration of intravenous ergometrine. In the first case, the second premature baby was presenting as a vertex and was successfully delivered spontaneously a few minutes later. The second infant in the next case was found presenting as a footling when the operator made an immediate vaginal examination and ruptured the membranes. Strong uterine contractions did not effect delivery and 8–10 minutes later under general anaesthesia a breech extraction was performed with difficulty on account of a contraction ring. The 3 pounds 10 ounces baby died at 55 minutes, presumably from anoxia. Following this experience, the operator kept the presenting part high with a hand in the vagina until a general anaesthetic was administered and the child was then successfully extracted, in the third case by breech extraction and in the fourth by forceps. One of these infants did well but the other, which was premature, had cyanotic attacks and was suspected of mongolism.

As the authors point out, the increasing use of second stage ergometrine to prevent post-partum haemorrhage will inevitably mean that on occasion it will be given before a diagnosis of twin pregnancy is made. Such therapy must potentially mean serious risk, especially if the second infant happens to present transversely, but foetal anoxia will be minimized if membrane rupture is, if possible, delayed by keeping the presenting part high until immediate delivery under general anaesthesia can be achieved.

Doreen Daley

234. **A Method of Induction of Labour in Pre-eclamptic Toxaemia and Hypertension of Pregnancy.**

By W. D. CUNNINGHAM. *Med. J. Aust.*, **1**, 904–907. June 12, 1954. 2 refs.

The condition of the cervix is considered favourable for induction of labour when it is at least half effaced, is one to two centimetres dilated, is in the pre-axial or mid-axial position and where the head is just at the level of the ischial spines.

If the condition of the cervix is unfavourable the author thinks that there is much to be gained by making it favourable so as to increase the chance of vaginal delivery.

To favourably alter the condition of the cervix the author advises daily digital dilatation over 3 or 4 days together with stripping of the membranes till it just admits 2 fingers. The position of the cervix in relation to the pelvic axis is important. After the thirty-sixth week the cervix may point towards the introitus. In 2 per cent of cases where it does not rotate forward or is not artificially assisted to do so then dystocia may occur.

As a result of the 3 to 4 days treatment the cervix is "ripened" or "primed"; and the patient is then moved to the labour ward where the membranes are further stripped or a high or low rupture is done. After one hour if labour has not commenced a course of pitocin injections is instituted.

If labour fails to commence, then further delay may become dangerous, and the entire problem should be reviewed carefully and attention given to the desirability of Caesarean section.

In 2 years 221 patients with pre-eclamptic toxaemia were treated. Induction was done in 104 and Caesarean section in 11. Ten of the inductions were excluded from the study because of unsatisfactory time recordings. Of the cases in which delivery was by the vagina forceps were required in 40. No infection of the genital tract occurred and there was no maternal mortality. Eight infants were lost.

S. Devenish Meares

235. **A Labour-Inhibiting Factor in the Liquor Amnii of Early Pregnancy.** (Ein geburtshemmender Faktor im Fruchtwasser der frühen Schwangerschaft.)

By S. BLOCH. *Gynaecologia, Basle*, **137**, 360. June, 1954. 32 refs.

Amniotic fluid obtained in early pregnancy from women and from cows has been shown to contain a factor which inhibits the onset of labour in mice. This factor disappears in liquor which is allowed to stand for 5 to 21 days. It is not present in liquor amnii collected during labour. The author refers to her earlier work in which she showed that colostrum contains a factor which induces abortion in mice (*Gynaecologia, Basle*, **121**, 204, 1946).

The labour-inhibiting effect of liquor amnii does not take place through the ovaries which do not show excessive luteinization.

Josephine Barnes

ANAESTHESIA

236. **Efocaine. Complications following its Use.**

By D. C. MOORE. *West. J. Surg., Obstet. Gynec.*, **61**, 635–638. Nov. 1953. 35 refs. 1 fig.

During the past 2 years a number of serious complications using this drug have been reported. Deaths from thrombosis of veins following injection into the veins have been reported and transverse myelitis following injection into intercostal nerves is not uncommon. Neuritis, cellulitis, post-operative haemorrhage and abscess formation have also occurred. In general the action of the drug is of the same order as alcohol and phenol and the author concludes that the injection of Efocaine is an unsafe procedure.

D. C. A. Bevis

237. **Risk from the Aspiration of Vomit during Obstetric Anaesthesia.**

By R. B. PARKER. *Brit. med. J.*, **2**, 65–69. July 10, 1954. 2 figs. 18 refs.

The author reviews the literature from 1937 on maternal deaths due to inhalation of vomit during anaesthesia, and adds a further 7 cases occurring in the Birmingham Maternity Hospital during the 10-year period, 1943–52. Premedication was by 1/75 or 1/100 gr. of atropine, followed by nitrous oxide, oxygen and ether. In 6 cases a forceps delivery was performed, but in 1 the patient died during Caesarean section. Two of the 7 patients recovered. Case 1 illustrated the "obstructive" type of lesion in which the inhalation of solid food causes acute asphyxia and heart failure. The other 6 cases illustrated the "asthmatic" lesion due to inhalation of liquid vomit. This type is probably the commoner in obstetric cases, where food is withheld, but the drinking of large quantities of fluid encouraged. Here vomiting occurred during the induction, but on continuing the anaesthetic the patient's condition appeared satisfactory. After an interval of 1 or 2 hours, tachycardia and cyanosis developed, with laboured breathing. Widespread adventitious sounds were heard all over the chest, but there were no areas of collapse. It is suggested that the danger to life arises from the developing generalized bronchospasm which may occur when the effects of the anaesthetic have disappeared. If anoxia persists, widespread pulmonary oedema occurs.

Under prevention the author makes a further plea for local anaesthesia where possible. If fluids have been taken recently, the wide-bore stomach tube is essential.

The importance of a tilting table and mechanical sucker is emphasized. A transparent face-piece and cuffed intratracheal tube are useful.

When vomiting occurs during induction, the anaesthetist will only continue the anaesthetic if no aspiration has occurred. If respiratory spasm occurs on recovery from the anaesthetic, bronchoscopy must be performed with the patient reanaesthetized. Oxygen is essential, probably with helium, and antispasmodics should be given—intravenous aminophylline or adrenaline, but possibly intravenous A.C.T.H.

Eileen Wilson

238. **Cardiac Arrest under Anaesthesia During Induction of Labour With "Pitocin" Drip.**

By M. LESSER and G. A. EASON. *Brit. med. J.*, **2**, 79–80. July 10, 1954. 7 refs.

The authors, from the Chester City Hospital, record a case of cardiac arrest which resulted from the administration of cyclopropane anaesthesia. The patient had been examined vaginally under anaesthesia for antepartum haemorrhage, and the membranes ruptured. The anaesthetist then washed away the cyclopropane with nitrous oxide and oxygen, and after 5 minutes, when the patient was recovering consciousness, a pitocin drip was started—30 units of pitocin being added to the remains of a 1,000 ml. saline bottle. Cardiac arrest occurred almost immediately.

The authors feel that the small amount of vasopressin present as an "impurity" in the pitocin was still sufficient in combination with cyclopropane to cause cardiac arrest, and the combination should be avoided. They also suggest that a pitocin drip may be dangerous in those who may have coronary disease, i.e. those over 40 years of age.

Eileen Wilson

LACTATION

239. **Clinical and Chemical Studies in Human Lactation. VII. The Effect of Differences in Yield and Composition of Milk on the Infant's Weight Gain and the Duration of Breast-feeding.**

By F. E. HYTTEN. *Brit. med. J.*, **1**, 1410–1413. June 19, 1954. 2 figs. 16 refs.

The author investigated 167 women delivered in the Aberdeen Maternity Hospital. The milk was sampled (as described in previous papers) on the seventh day of lactation. 148 of these patients and babies were followed up for 13 weeks.

Only the 7th day yield and fat content were related to the clinical findings, and by multiplying them the total fat output for 24 hours was used.

The infants' weight gain in hospital from the 3rd to 7th day was studied. Where the total fat output was less than 5 g., only 20 per cent gained more than 4 ounces. When the fat output was 20 g., or more, 58 per cent gained more than 4 ounces.

Of the 148 mothers followed up for 13 weeks, 23 were excluded where breast feeding had been discontinued for reasons unrelated to poor lactation. Of the remaining 125, 51·2 per cent stopped breast feeding before the 13th week, because "lactation failed".

These patients were grouped according to the 7th day fat output. In the highest group of 20 g. or more, 80 per cent breast-fed for 13 weeks, compared with only 18 per cent in the lowest fat output group. Both yield and fat content on the 7th day were associated separately with the duration of breast feeding.

Eileen Wilson

INFANT

240. **Sex Incidence of Congenital Malformations.** (Frequenza dei sessi nelle malformazioni congeniti.)

By G. ANGELI. *Minerva Ginec.* April 30, 1954. 2 tabs. 16 refs.

Various contrary opinions have been given as to the influence of sex on the liability of an infant to congenital deformities and malformations. In this article, the statistics of the Clinic at Perugia are analyzed, involving 83 infants over a period of 47 years. Of these 43 were male and 40 female. It is noted that for the first half of this period from 1906 to 1928 there were 7 males and 18 females, whilst from 1928 onwards there were 36 males against 22 females.

It is concluded that numbers probably tend to level out as in pure chance. The only point of note in this series is that multiple deformities were more common among the female infants, numbering 31 as against 18 in the males.

W. C. Spackman

241. **The Treatment of Erythroblastosis Foetalis, with Rh Hapten. Review of a Hundred Cases.**

By B. B. CARTER. *Lancet*, **1**, 1267–1269. June 19, 1954. 2 tables. 14 refs.

The author briefly reports the results obtained in sensitized Rh-negative pregnant women injected intramuscularly with a blood fraction. This fraction (Rh Hapten) is obtained from Rh-positive (pooled C D E positive) human red cells. When mixed with potent anti-D serum and incubated for 30 minutes it absorbs a high percentage of the Rh antibodies. The treatment is used primarily for Rh-negative sensitized women rather than for the newborn infants. It is commenced as early in pregnancy as possible. No reactions have been observed other than local soreness at the site of the intramuscular injections. It is claimed that the maternal antibody titres have shown a consistent falling off under treatment with the red cell fraction. Of the 100 women treated, 15 had Rh-negative infants. [It is difficult to understand how these became sensitized.] Of the remaining 85, there were 29 women with no previous history of an erythroblastotic child who were delivered of 27 normal babies and 2 babies who died after birth, and there were 56 women with a history of erythroblastotic children or transfusion whose pregnancies ended in 18 stillborn infants and 38 live infants. Eight of these died leaving a total of 30 surviving infants, 9 of whom received transfusion treatment. These figures give a mortality of 7 per cent for

babies whose mothers became sensitized to Rh in the current pregnancy and a mortality of 47 per cent for babies whose mothers had erythroblastotic children previously. The author concludes from comparisons with other published series that treatment of the expectant mother with red-cell fraction increases the number of normal babies.

H. H. Fouracre Barns

242. **Pulmonary Hyaline Membranes—Preliminary Report on Experimental Production.**

By L. E. LAUFE and S. S. STEVENSON. *Obstet. and Gynec.*, **3**, 637–641. June 1954. 1 plate. 4 refs.

Into the lungs of 40 guinea-pigs the authors injected plasma and amniotic fluid. In a few of these the picture of the pulmonary hyaline-like-membrane syndrome was produced, the animals developing symptoms similar to those seen in the newborn human infant. Microscopically, atelectasis, vascular congestion and a hyaline membrane were seen. The authors suggest the following sequence occurs in the human disease.

1. The newborn infant aspirates amniotic fluid.
2. The infant's lungs exude a fluid of high protein content as a result of vagal injury, irritation from amniotic fluid, administered oxygen, or some other noxious influence.
3. The amniotic fluid speeds clotting of this exudate which forms a hard membrane.
4. Plugs of the clotted material cause extensive atelectasis.

J. G. Dumoulin

243. **On Hyaline Membrane and Atelectasis of the Lungs of the Newborn.** (Uber hyaline Membranen und Atelektasen der Neugeborenen-Lunge.)

By FRITZ REUTTER. *Gynaecologia, Basel*, **137**, 367. June 1954. 5 figs. 33 refs.

Hyaline membrane affects chiefly premature infants weighing 1,000 to 2,500 grammes and occurs mainly between 2 hours and 2 days after birth. A description is given of the pathological anatomy and the clinical features. The infant is well at birth with a good colour in some cases, symptoms developing some hours later. In others, signs of asphyxia are present at birth. Some of these apparently recover, only to relapse into asphyxia, while in others there is no free interval. Hyaline membrane is a factor in a vicious circle of asphyxia, increasing already existing asphyxia and resulting in secondary atelectasis.

The nature and origin of hyaline membrane is fully discussed but no advice is given regarding treatment.

Josephine Barnes

244. **Retrolental Fibroplasia and Oxygen Therapy.**

By J. T. LANMAN, L. P. GUY and J. DANCIS. *J. Amer. med. Ass.*, **155**, 223–226, May 15, 1954. 15 refs.

Retrolental fibroplasia (RLF) is now first among the causes of blindness in children in the United States and is the foremost problem other than death itself in the care of premature infants. The authors have investigated the association of RLF with intensive oxygen therapy under controlled conditions at the Bellevue Hospital Premature Nursery, New York University.

At first oral administration of oestrogen was included in the investigation, but it was found to have no influence on the neonatal mortality rate or on the incidence of RLF. Comparison was therefore made on two groups of infants, one in which the oxygen concentration given was high (69 per cent), and the other in which it was low (38 per cent). In the high concentration group infants were kept in oxygen for a minimum of 2 weeks or until they reached a weight of 1,500 g. (3·3 pounds) when therapy was discontinued abruptly. In the low concentration group oxygen was discontinued at least once daily and only resumed for the reappearance of cyanosis. Incubator care was identical in both groups and funduscopic examinations were carried out once weekly.

Of the 86 infants studied 21 died before the age of 3 months and 1 could not be followed up. The results of the remaining 64 infants are recorded. Eight cases of severe, bilateral, irreversible, cicatricial RLF were found in 36 surviving infants of the high oxygen concentration group. No case of RLF was found in the 28 surviving infants in the low oxygen concentration group.

The mechanism of injury is suggested by animal experiments in which excessive oxygen damages developing retinal blood vessels. Vitreous changes and retinal detachment follow. Some conflicting reports are discussed and the authors recognize that other agents may be capable of producing RLF for occasional cases occur in infants who have never received oxygen. They believe however, that RLF is directly related to the excessive administration of oxygen and can be controlled by severely limiting oxygen therapy in premature infants. In this premature unit oxygen is now given only to definitely cyanotic infants, and then only at concentrations below 40 per cent. Such restriction has not appeared to be harmful, and in retrospect the liberal administration of oxygen did not show any significant lowering of the mortality rate in the premature infants.

D. W. James

245. **Anaemia from Bleeding of the Foetus into the Mother's Circulation.**

By B. CHOWN. *Lancet*, **1**, 1213–1215. June 12, 1954. 1 table. 5 refs.

This is a short article reporting one case in which the baby was born with severe anaemia. The haemoglobin was 7·8 g. per 100 ml. and red cells 2,300,000 per c.mm. The baby was Rh-positive (the mother was Rh-negative) but Coombs'-negative. The baby was given a transfusion and recovered. From haematological studies carried out on the mother the author estimates that some 5–10 per cent of the red cells were derived from the foetus. Whereas the mother's blood contained no antibodies during pregnancy and at the time of delivery, antibodies were detected on the 20th day of the puerperium. It is suggested that foetal-maternal transfusion may cause, in addition to non-haemolytic anaemia of the newborn, foetal death, atypical toxaemia and rarely jaundice of pregnancy.

H. H. Fouracre Barns

GYNAECOLOGY

246. **Description of Colpophotography and its Uses.** (Fortschritte der Kolpophotographie und ihre Bedeutung.)

By H. J. Wespi and W. Lotmar. *Gynaecologia, Basel*, **137**, 281. June 1954. 22 figs. 36 refs.

A description is given of an apparatus by which it is possible to perform colpophotography. By its use, photographs of the portio vaginalis enlarged 0·5, 1·1 and 3·5 times may be obtained. The exposure is made by illumination with an electric flash and blurring caused by movement of the patient or the apparatus is overcome by an exposure of 1/500 to 1/2000 of a second. By relatively simple modifications the apparatus can be used as a monocular colposcope or as a colpo-projector.

The technical photographic problems involved are discussed and illustrations are given showing the application of the instrument not only in photographing the cervix uteri but also lesions of the eyes and teeth and in recording fingerprint patterns.

Josephine Barnes

247. **Varicocoele in Groups of Fertile and Subfertile Males.**

By J. K. Russell. *Brit. med. J.*, **1**, 1231–1232. May 29, 1954. 15 refs.

The purpose of this investigation was to correlate the incidence of varicocele and fertility. Only in those cases where the author noted himself that there was palpable and visible enlargement of the pampiniform plexus, was the diagnosis made.

Group 1 comprised 51 men of high fertility, proved by a large family as well as by a high sperm count. None had a varicocele.

Group 2 consisted of 48 men whose wives had recently had their second, third or fourth child. Sperm counts ranged from 37 to 250 million per ml. There were two cases of varicocele. (2 per cent for Groups 1 and 2 combined.)

Group 3 included 144 men examined at a fertility clinic because their wives had had no children. All sperm counts were above 75 million per ml. and 2 of the men had a varicocele (1·4 per cent).

Group 4. These 119 husbands of infertile wives had sperm counts below 50 million per ml. and 9 of them had a varicocele (9·2 per cent).

As the condition tends to affect young men and may regress in later life, age analysis was undertaken and proof obtained that the more frequent incidence of varicocele in the fertile than in the subfertile men could not be explained by their being in different age groups. There was evidence to support the view that a varicocele persisting beyond the age of 30 is particularly apt to be associated with poor quality semen, but the study gave no information of the proportion of varicoceles that persist beyond that age.

Particularly as surgical intervention is not without its dangers, no plea is made for more active treatment of varicoceles but the traditional attitude that the condition is innocuous is challenged and the need for more investigation into its natural history and effect on fertility is stressed.

Doreen Daley

248. **Blood Groups and Gynaecological Cancer.**

By E. Krokfors and O. Kinnunen. *Brit. med. J.*, **1**, 1305–1306. June 5, 1954. 3 refs.

Aird *et al.* (*Brit. med. J.*, **1**, 799, 1953) have reported statistics showing a greater frequency of blood group A and a correspondingly lower frequency of blood group O in patients with cancer of the stomach than in the general population.

A similar study has been made of the distribution of blood groups in 300 patients with gynaecological cancer treated at the Women's Clinic in Helsinki which deals with most of the major gynaecological work of Finland. A control series was obtained from non-malignant cases at the hospital and results also correlated with data published regarding the blood-group distribution in the general population in Finland.

Results showed a clearly lower frequency of blood group A and a higher incidence of group O in the gynaecological cancer group, whether all malignant cases or just those with uterine carcinoma were considered. This difference from the control group appeared most distinctly in the youngest patients studied.

Doreen Daley

249. **Malignant Chorionepithelioma—Use of Hysterosalpingography as a Diagnostic Aid.**

By A.-L. Alha. *Ann. chir. gynaec. fenn.*, **43**, 136–141. 1954. 4 figs. 6 refs.

The author describes a case of chorionepithelioma secondary to hydatidiform mole. Fourteen days after curettage of the mole uterine bleeding was still present and the A–Z was positive. A tentative diagnosis of chorionepithelioma was made and in order to avoid a further curettage hysterosalpingography was carried out. This revealed a filling defect in the uterus and on the strength of this a total hysterectomy and bilateral salpingo-oöpherectomy was carried out. The growth was chiefly intramural and the author suggests hysterosalpingography as a possible and safer means of diagnosis than curettage.

D. M. Sheppard

250. **The Sites of Metastasis in Carcinoma of the Cervix.**

By R. R. de Alvarez. *West. J. Surg. Obstet. Gynec.*, **61**, 623–627. Nov. 1953. 10 refs. 4 figs.

The author (working in the University of Washington) discusses the metastasis of primary cervical carcinoma in 71 patients, all metastases being proved by biopsy, operation, radiology or autopsy. He finds that the lymphatic spread is mainly retroperitoneal but a surprisingly larger number of cases of supraclavicular involvement occurred (20 per cent) while relatively few developed inguinal metastases (11 per cent). Metastasis in bone occurred frequently, the most common being the lumbar spine; extension of the primary growth into the bony pelvis is very infrequent. The visceral organs most

frequently involved were the lungs, liver and colon. This metastasis shows no relationship to the degree of the local pelvic disease.

Only 15·5 per cent of all the metastases were suspected clinically, the most difficult being to brain, bone and lungs; the value of radiological examination is stressed in searching for these distant metastases. The degree of local spread may be determined by the examining finger but growth out of reach, especially round the ureter, may be discovered by pyelography and the determination of the alkali reserve and the blood urea concentration.

[This is a useful paper and should be read in its entirety.]

D. C. A. Bevis

251. **Cytological Follow-up Examination of Irradiated Cervical Carcinomata.** (Die Cytodiagnostik bei Nachuntersuchungen bestrahlter Collumcarcinome.)

By P. STIEPER. *Arch. Gynäk.*, **184,** 643–653. May 1954. 4 figs. 1 table. 17 refs.

This is a record of 549 women 3 months to several years after radium or X-ray treatment or post-operative ray-treatment for carcinoma of the cervix who were followed up between 1951 and 1953. One single smear examination only was carried out on each patient.

Of these 549 patients, 61 had a local recurrence or vault secondaries. Of the 488 patients without local recurrence, 454 had negative smears and 34 or 7 per cent were wrongly labelled "suspicious". Of the 61 patients with local recurrence or secondaries, 48 had "suspicious" and 3 "doubtful" smears and 10 or 16·8 per cent were "false negatives".

The author argues that the value of cytodiagnosis lies in cancer detection rather than in confirmation of clinically obvious malignancies. Reviewing his material from this point of view, his conclusions are most depressing. Of 464 negative smears 10 or 2·2 per cent were found to be false, whereas of 76 suspicious smears 28 or 36·8 per cent were not confirmed histologically. If over one-third of all the positive smears were wrong, the value of smear investigations was indeed insignificant. The question arose, however, whether at least a proportion of these smears labelled "false positive" did not come from patients with a micro-recurrence which was as yet clinically unrecognizable and therefore, the biopsy had been taken from an area free from disease. Graham and Meigs had described 7 such cases, and indeed 6 of the author's cases (detailed case histories are given) with initial positive smear and negative biopsy reports showed histologic confirmation of malignant recurrence 3½ to 18 months later. The author concluded that, in view of the high proportion of false positive smears, a single abnormal smear must be regarded as meaningless; if "follow-up" smears and biopsy findings are negative, no importance should be attached to the isolated cytological report. If, on the other hand, the smears continue to show abnormal cells, colposcopic examinations and extensive biopsies should be carried out.

E. Wachtel

252. **Polycystic Ovaries.** (Über kleincystische Ovarien.)

By C. SVENSTRUP. *Acta obstet. gynec. scand.*, **33,** 211–227. 1954. 75 refs.

There is wide divergence of opinion about the aetiology and the significance of multiple small cysts in the ovaries. Exaggerated physiological processes (atresia), pelvic hyperaemia including venous congestion due to retroflexion, pelvic tumours, "varicocele" and even "stress", pelvic peritonitis and hormonal dysfunction have all been held responsible for this condition. Symptoms associated with polycystic ovaries comprise dysfunctional metrorrhagia, hypo-oligomenorrhoea, amenorrhoea, intermenstrual bleeding, dysmenorrhoea, pelvic pain, "Mittelschmerz", deep dyspareunia, leucorrhoea and sterility. Unilateral oöphorectomy, wedge-resection from one or both ovaries, splitting of the ovaries, partial ligature of mesovarian vessels, and extroversion have been described as more or less successful methods of treatment.

The author studied 72 cases in which polycystic ovaries were found at operation at the gynaecological department of Odense (Denmark) Municipal Hospital. Cases in which there was co-existent disease such as salpingitis, endometriosis, pelvic tumours, and those in which there was a history of genital infection were not included in this series.

The average age of the patients was 28. Fifty per cent of these 72 patients were described as nervous or neurasthenic, in 49 per cent there was genital hypoplasia and/or male distribution of hair, and 25 per cent were sterile. In 50 per cent there were menstrual abnormalities. In 54 patients of this series "conservative" operations (unilateral or bilateral wedge-resection, or unilateral oöphorectomy) were performed; 40 per cent of these patients became free from complaints, 16 per cent improved, and 44 per cent did not improve or got worse; 7 out of the 17 sterile women of this group became pregnant within 12 months of the operation. In 18 patients hysterectomy with unilateral or bilateral oöphorectomy was considered necessary; 8 of them became free from complaints, 3 improved and 7 did not improve.

The author arrives at the conclusion that polycystic ovaries do not constitute a clinical entity, but that there may be a congenital predisposition to this abnormality.

N. Alders

253. **Carcinoma of the Fallopian Tube.** (El Carcinoma de la Trompa.)

By R. SAMMARTINO and D. CALANDRA. *Obstet. Ginec. lat-amer.*, **11,** 357–367. Sept. 1953. 5 figs. 1 table. 24 refs.

The authors report 6 cases of primary carcinoma in the Fallopian tube, "the least common site for neoplasms in the genital organs". They state that only 660 such cases have been reported.

Except for 1 patient of 70 years, the ages of the patients ranged from 24 to 61; they were all parous. No syndrome indicative of the diagnosis could be inferred from the case histories. In 4 of them post-menopausal bleeding was the first symptom, and lower abdominal pain developed in only 2 of these patients. In one of them, the

Papanicolaou vaginal smear was positive, yet at operation the carcinoma was found to be localized in one tube, both ovaries were normal and no metastases were seen. The remaining 2 cases reported were pre-menopausal: 1 (aged 42 years) experienced amenorrhoea for 8 months before the onset of pain, and the other patient (aged 24 years) did not appear to experience any menstrual irregularity.

At operation, the carcinoma was found to be unilateral in each case. In only 2 were any metastases seen. In a series of so few cases collected over a period of several years, it is impossible to assess a mortality rate: the authors report 4 alive at the time of publication, the longest follow-up being 8½ years, and another 5 years. They report 2 deaths within a few months of operation, yet neither of them was thought to have metastases.

The authors conclude by a review of the literature from which they quote that 75·1 per cent of the reported cases presented a unilateral carcinoma, 50 per cent were sausage-shaped macroscopically and 95 per cent appeared to grow without destroying the lumen of the Fallopian tube.

John F. Foulkes

254. **Further Studies on Experimental Endometriosis.** By R. B. Scott, R. W. TeLinde and L. R. Wharton. *Amer. J. Obstet. Gynec.*, **66**, 1082–1103. Nov. 1953. 1 table. 16 figs. 26 refs.

The validity of Sampson's original theory of the source of external endometriosis depended on whether endometrial cells shed during menstruation and extruded through the tube into the peritoneal cavity were viable or no. The experiments of Heim on monkeys in 1928 suggested that they were not. In one the uterus was opened at laparotomy during menstruation and some of the contents withdrawn and placed in the pouch of Douglas; in the other the fundus was removed and left open so that the monkey menstruated into the peritoneal cavity, but in neither case did any endometriosis develop. The present authors suspected that Heim's period of observation was too short, so they repeated her latter experiment and did autopsy studies 2½ years later, when they found extensive endometriosis. In further experiments, an account of which was published in 1950, they surgically altered the uterus in 10 monkeys to permit menstruation into the abdominal cavity and endometriosis developed in 5. Endometriosis could not be caused by injection of circulating blood withdrawn during menstruation thus disposing of the possibility that the blood contained some irritant that could induce metaplasia of the peritoneal epithelium into endometrial tissue.

To determine whether the presence of coelomic (peritoneal) epithelium was necessary for development of endometriosis, the cervix was cut across, denuded of peritoneum and then implanted into the anterior abdominal wall into which alone the menstrual discharge could then take place. In each of 3 such experiments endometriosis was found in the rectus muscle or surrounding tissue in the abdominal wall. As it arose in spite of the implanted cervix being denuded of its peritoneal coat it could not have been due to mere metaplasia of peritoneal cells as claimed by Meyer.

These experiments seem finally to establish the validity of Sampson's hypothesis that external endometriosis could arise from extrusion through the tube of endometrial cells shed during menstruation. In his later years he suggested that it could arise from metaplasia of tubal epithelium, especially in a tubal stump, or at the junction of tubal mucosa and peritoneum, but the present authors seem to have disposed of this possibility by transplanting endosalpingeal tissue into ovary, uterus, bowel and abdominal wall. Biopsies 119 to 683 days later showed no evidence of endometrial tissue in any, endosalpingeal tissue alone being identified.

The metaplasia of pelvic peritoneum or other tissues in the pelvis is considered the least likely of all hypotheses for the histogenesis of external endometriosis.

F. J. Browne

OPERATIONS

255. **Transverse Approach to Lower Abdomen.** By W. Tenenblatt and T. A. Cook. *Obstet. and Gynec.*, **3**, 627–630. June 1954. 1 fig. 12 refs.

The transverse lower abdominal incision through the skin and all layers of the abdominal wall is no new approach to the pelvis. The authors write of its use in over 100 cases. They claim that bleeding is slight and the deep epigastric vessels can be ligated after cutting across the rectus muscles. In closing the wound it is important to approximate carefully the peritoneal edges and the fascial sheaths. No attempt is made to approximate the muscles. The wound, in healing, forms a fibrous intersection which is strong. This approach gives an excellent exposure with no great risk of post-operative hernia. The authors consider that more surgeons would benefit by overcoming the psychological resistance to cutting across the recti muscles. *J. G. Dumoulin*

256. **Simple Total and Subtotal Amputation of the Uterus and Porro's Operation as Obstetrical Procedures.** (Einfache totale und subtotale Uterusamputation und Porro'sche Operation unter der Geburt.)

By K. Niemineva and P. Erb. *Gynaecologia, Basle*, **137**, 306. June 1954. 17 refs.

Statistics are given of the results of Porro's operation as performed in the University Clinic at Basel and at two University Clinics at Helsinki. Porro's operation has been performed for the following main indications: Placenta accreta, ante-partum haemorrhage, multiple fibroids, infection and rupture of the uterus. It is noted that infection is now rarely an indication.

The maternal mortality of this operation has amounted to about 18 per cent in the last 25 years. In the last 10 years, however, there has only been 1 maternal death in 10 operations performed in the Basel clinic.

Experience in both clinics has led to the view that Porro's operation is only rarely indicated and the authors do not agree with current views in the United States which favour more frequent performance of this operation. *Josephine Barnes*

257. **Abdominal Total Hysterectomy: A Helpful Point of Technique.** (Su di un particulare di tecnica nell'esecutione dell' isterectomia totale.)

By W. INGIULLA. *Minerva Ginec.*, 51–52. April 15, 1954. 2 figs.

A step in the operation is described which has been found useful in the Clinic at Florence; it probably originates from Meigs's clinic in Boston. After dividing the round ligaments and infundibulo-pelvic folds, the uterus is drawn well forward so as to put on stretch the utero-sacral ligaments which are then clamped and divided close to the rectum. This renders access to the base of the broad ligaments easy, and the uterine arteries with their cervical branches are easily caught in curved clamps.

A further idea is to run a continuous suture along the anterior and posterior cut margins of the vagina separately (for haemostasis), but to leave a gap down into the vagina between the two edges. This gap allows any effusion to drain down and in practice is devoid of risk of infecting the operation area provided simple disinfection measures are taken in the pre-operative preparation of the patient.

W. C. Spackman

258. **Management of the Surgically Injured Ureter.**

By E. K. LANDSTEINER. *Surg. Gynec. Obstet.*, **98**, 653–661. June 1954. 6 figs. 16 refs.

The steadily increasing number of radical gynaecological and general surgical procedures performed in the pelvis has resulted in an ever-increasing number of cases of ureteral injury. In most of these the lower third of the ureter is involved. Twenty cases of low ureteral injury seen by the Urological Service of the Rhode Island Hospital during the past 5 years have been studied and form the basis of this report.

There are several principles which serve as useful guides, not only for treatment, but for the prevention of injury to the ureter:

1. Pre-operative catheterization of the ureters would go far to reduce the number of ureteral injuries and, failing this, pre-operative intra-venous urograms at least should be performed on all patients about to undergo major pelvic surgery.
2. Recognition of ureteral injuries at the time of the initial surgery is of the greatest importance.
3. Every effort should be made to solve the problem without resorting to nephrectomy.

Immediate Treatment of Ureter Injured at Operation

The ligated ureter is the simplest form of ureteral injury to deal with. Removal of the suture and retrograde ureteral catheterization with a plastic catheter are all that is required. An angulated ureter and an incised ureter can be treated in a similar fashion, except that in the latter it is important that the area of incision be drained extra-peritoneally. A crushing injury with a clamp is no different from complete severance of the ureter. End-to-end anastomosis or implantation of the proximal end into the bladder are the two choices in this situation. The author has favoured the latter type of repair as it is relatively easy to perform and is less prone to stricture formation.

Where the ureter is severed in its lower third in such a way that neither anastomosis nor bladder implantation is possible, a plastic bladder flap can be utilized successfully to bridge the gap and thus save the kidney. The technique of this procedure is described and illustrated in considerable detail.

Delayed Treatment of Ureter Injured at Operation

Unilateral ureteral ligation often goes unnoticed, particularly if there is no pre-existing renal infection and the other kidney is normal.

On the other hand, incomplete obstruction of one ureter, caused by a partially tied suture or by angulation, will usually become apparent by the development of a renal infection or pain and can be evaluated by intravenous urogram.

Anuria following major pelvic surgery demands early cystoscopic investigation to rule out bilateral ureteral obstruction. Where both ureters have been ligated nephrostomy is recommended, followed, at a later time, by a plastic procedure to the ureters.

In the author's series all cases were treated successfully without mortality, 9 by reimplantation of the ureter in the bladder, 2 by anastomosis, 3 by the utilization of a plastic bladder flap and in only 3 was nephrectomy necessary.

Throughout this article the importance of extraperitoneal drainage of the site of incision, repair, anastomosis or implantation is stressed.

John P. Erskine

259. **Bladder Dysfunction Following Gynaecological Surgery.**

By E. J. BOMZE. *West. J. Surg. Obstet. Gynec.*, **62**, 325–328. June 1954. 3 refs.

The author reviews his results following gynaecological operations on 121 patients, 74 of whom had abdominal procedures. Twenty-five patients had difficulty in micturition, an incidence of 20 per cent, 22 of whom had had vaginal operations. The largest number were patients who had anterior colporrhaphy operations, either alone or with other operations. It was found that the presence or absence of pre-operative urinary complaints and the type of anaesthetic used had no influence on the occurrence or severity of the bladder upset. The period of recovery of the bladder was 6 days or more and the author suggests that injury of the bladder wall during operation is the main cause of trouble. Sharp dissection should be used in anterior colporrhaphies and a wide bore, self-retaining catheter should be put into the bladder at the end of the operation; if the bladder did not receive rough handling, this may be removed after 24–48 hours. Instillation of mercurochrome, argyrol, etc., did not prevent retention. The patient may be instructed to release the catheter whenever she has the urge to micturate and this proved especially useful after the 4th–5th post-operative day; before this the catheter should be draining continuously.

D. C. A. Bevis

UROLOGY

260. **The Nonoperative Treatment of Stress Incontinence in Women.**

By L. H. WHARTON. *Amer. J. Obstet. Gynec.*, **66**, 1121–1130. Nov. 1953. 15 refs.

The author got good results by exercises in cases of stress incontinence which were or were not associated with prolapse or where operative cure of the prolapse did not cure the incontinence. The exercises consist in the voluntary and strong contraction of the muscles that stop or prevent the flow of urine. The patient is told to make the same effort as when she prevents the flow of urine if she should have the desire to void under unpropitious circumstances. This contraction also involves the vaginal muscles and rectal sphincters. The exercise should be repeated 15 times 3 times a day. Generally within 1 month benefit is evident. No perineometer, such as that devised by Kegel (*West. J. Surg. Obstet. Gynec.*, **57**, 527, 1949) was used; without the perineometer the exercises can be carried out wherever the patient happens to be. Of 63 cases, 30 per cent were cured, a result as good as that got by Kegel with his perineometer.

F. J. Browne

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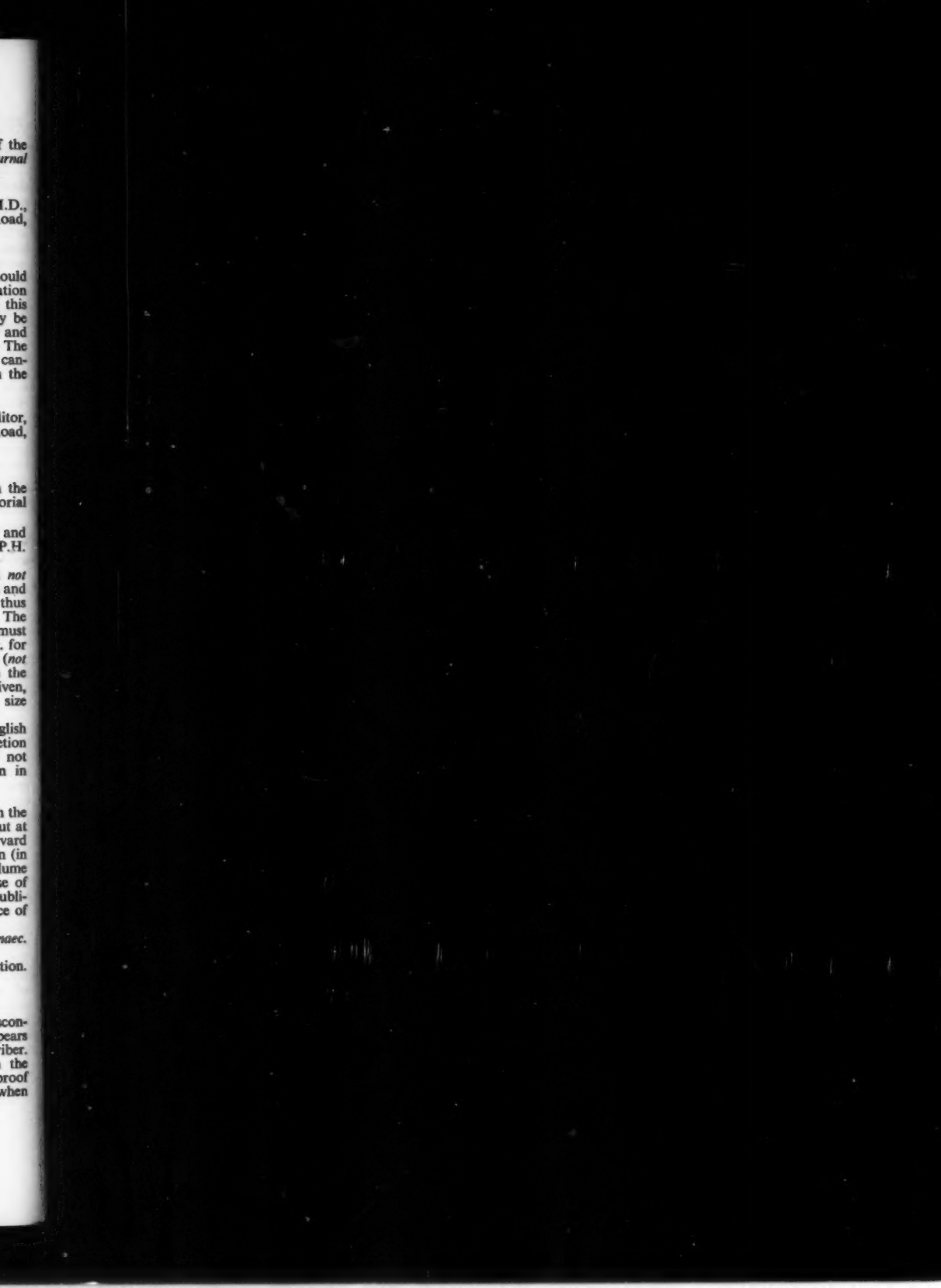
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